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Modelos Matemáticos em Imunologia e em Investigação & Desenvolvimento

Departamento de Matemática
Faculdade de Ciências da Universidade do Porto
junho de 2014

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Abstract

In this PhD thesis in Applied Mathematics, Dynamical Systems and Game Theory are applied to Biomedical Sciences and Economical Sciences. The subject of Immunology is covered in the models with Regulatory T cells and the Patent Licensing is studied in a Cournot competition framework.

Asymmetry in Immune response models with Regulatory T cells: We analyse a model of immune response by T cells (CD4), where regulatory T cells (Tregs) act by inhibiting IL-2 secretion. We study an asymmetry reflecting that the difference between the growth and death rates can be higher for the active T cells and the active Tregs than for the inactive T cells and inactive Tregs. We present explicit formulas, both approximate and exact, that give the concentration of T cells as a function of the concentration of Tregs and explicit formulas that relate the antigenic stimulation of T cells, the concentration of T cells and the concentration of Tregs. The relation between the antigenic stimulation of T cells and the concentration of T cells is an hysteresis that is unfolded when some of the parameters are changed. We also consider a linear tuning between the antigenic stimulation of T cells and the antigenic stimulation of Tregs. In this case, we also have obtained explicit formulas, both approximate and exact, relating the antigenic stimulation of T cells, the concentration of T cells and the concentration of Tregs. With these, we can explain the appearance of an isola and a transcritical bifurcation.

Strategic optimization in R&D Investment: We use d'Aspremont and Jacquemin's strategic optimal R&D investment in a duopoly Cournot competition model to construct myopic optimal discrete and continuous R&D dynamics. We show that for some high initial production costs, the success or failure of a firm is very sensitive to small variations in its initial R&D investment strategies.

Keywords: Equilibria, hysteresis, bifurcation, ODE model, immunology, T cells, Tregs, secretion inhibition, asymmetry, death rates, strategic R&D, Cournot duopoly model, patents.

Resumo

Nesta tese de Doutoramento em Matemática Aplicada, aplicam-se Sistemas Dinâmicos e Teoria de Jogos às Ciências Biomédicas e às Ciências Económicas. No âmbito da Imunologia são estudados modelos com células T reguladoras e o Licenciamento de Patentes é estudado numa competição de Cournot.

Modelos assimétricos de resposta imunitária com células T Reguladoras: É analisado um modelo de resposta imunitária por células T (CD4), no qual as células T reguladoras (Tregs) atuam inibindo a secreção de IL-2. É estudada uma assimetria que reflete que a diferença entre a taxa de proliferação e de mortalidade pode ser maior para as células T ativas e Tregs ativas do que para as células T inativas e Tregs inativas. Apresentam-se fórmulas explícitas, aproximadas e exatas, que permitem obter a concentração de células T em função da concentração de Tregs e fórmulas explícitas que relacionam o estímulo antigénico de células T a concentração de células T e a concentração de Tregs. A relação entre o estímulo antigénico de células T e a concentração de células T é uma histerese que se desdobra quando alguns dos parâmetros são alterados. Também se considerou uma relação linear entre o estímulo antigénico das células T e o estímulo antigénico das Tregs. Também neste caso se obtiveram fórmulas explícitas, aproximadas e exatas, relacionando o estímulo antigénico de células T a concentração de células T e a concentração de Tregs. Estas permitem explicar o surgimento de uma ilha e uma bifurcação transcrítica.

Otimização estratégica em investimentos em I&D: Usa-se a otimização estratégica em investimentos em I&D de d'Aspremont e Jacquemin num modelo de competição de Cournot em duopólio para construir dinâmica discreta e contínua de ótimos míopes em I&D. Mostra-se que para custos iniciais elevados, o sucesso ou o fracasso de uma das empresas é muito sensível a pequenas variações na estratégia inicial de investimento em I&D.

Palavras chave: Equilíbrios, histerese, bifurcação, modelo com equações diferenciais ordinárias, imunologia, células T, células T reguladoras, inibição da secreção, assimetria, taxas de mortalidade, I&D estratégico, modelo de duopólio de Cournot, patentes.

dedicated to Marcelo and Luana

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Contents

List of Tables

List of Figures

Chapter 1

Introduction

This thesis is the result of two different investigation projects I have been involved with. During my PhD in Applied Mathematics I was able to develop my knowledge in Dynamical Systems and Game Theory. These Mathematical concepts were applied to two distinct areas of knowledge that I knew little in the beginning of my PhD (and I still have much to learn about them): the Biomedical Sciences and the Economical Sciences.

In Chapter 2 we study a model of immune response by T cells, with the presence of Tregs presented in Burroughs et al. (2006) and further studied in Burroughs et al. (2008, 2011a,b,c,d) and surveyed in Pinto et al. (2010). In particular, we analyse here the asymmetry introduced in Burroughs et al. (2011b). In this model, cytokine dependent growth exhibits a quorum T cell population threshold that determines if immune responses develop on activation, Burroughs et al. (2006, 2008). Secretion inhibition by Tregs manipulates the growth dynamics and effectively increases the quorum threshold, Burroughs et al. (2006, 2008), i.e. to develop immune responses a higher number of T cells need to be activated. Thus Treg induced secretion inhibition can provide a mechanism for tissue specific regulation of the balance between suppression (control) and immune responses, a balance that can be varied at the local tissue level through the regulation of the local active Treg population size in order to protect the tissues against autoimmunity, Burroughs et al. (2008, 2011a,b,c,d); Pinto et al. (2010). The asymmetry is modeled by considering that the secreting T cells have a lower death rate than the non secreting T cells and that the active Tregs also have a lower death rate than the inactive Tregs, thus mimicking the effect of the memory T cells. With this asymmetry, the antigenic stimulation of the Tregs is able to control locally the population size of Tregs, and that there is an improvement of the efficiency of the immune responses, Pinto et al. (2010); Burroughs et al. (2011a,b,c,d). The results presented in Chapter 2 are contained in our papers Figueiredo et al. (2014); Oliveira

et al. (2014a,b,c). We have obtained an explicit formula that gives the approximate concentration of Tregs as a function of the concentration of T cells and the parameter values, and another explicit formula that gives approximately the antigenic stimulation of T cells as a function of the concentrations of Tregs and of T cells and the parameter values. Moreover, we were able to improve these results and to obtain exact formulas for both relations. The relation between the concentration of T cells and their antigenic stimulation is an S-shaped curve - an hysteresis - that contains a region of bistability bounded by two catastrophe points, the thresholds b_L and b_H of antigenic stimulation of T cells. We study the effects of the asymmetry parameters in the equilibria manifold and in the quorum T cell population thresholds and we observe that the hysteresis can be unfolded as in the symmetric case Burroughs et al. (2006, 2008). A positive correlation between the antigenic stimulation of T cells and the antigenic stimulation of Tregs enhances the protection against autoimmunity, Burroughs et al. (2011b). Here we present explicit formulas (approximate and exact) that explain the transcritical bifurcation found in Burroughs et al. (2011b). In a neighbourhood of parameters near this transcritical bifurcation the rate of variation of the level of stimulation determines if an immune response appears of if the Tregs maintain control when the antigenic stimuli increase, Pinto et al. (2010).

Investment in Patent Licensing is an active subject of the Economical Sciences. In Chapter 3 we study a model where two firms invest in Research and Development (R&D) to reduce their production costs, while in Cournot competition, with our results published in Ferreira et al. (2012). Here we continue the studies published in the papers Ferreira et al. (2009, 2010), but we study the investment function in d'Aspremont and Jacquemin (1988) instead of the investment function in Ferreira et al. (2009). This model is based on a two stages game, described by d'Aspremont and Jacquemin (1988) and analysed with a different investment function in Ferreira et al. (2009, 2010). The first subgame has at most three strategic optimal investment equilibria, only one of those, the competitive one, analysed by d'Aspremont and Jacquemin (1988). We consider a discrete and a continuous time dynamics (both myopic). We observe a high sensitivity to initial conditions, in particular in the continuous R&D dynamics.

Chapter 2

Immune response models with asymmetry

2.1 Introduction

The immune system protects the host from pathogen invasion. During such an invasion, T cells specific to the antigen proliferate and act to remove the pathogen. However, the immune system can erroneously target self antigens (autoimmunity) and cause tissue damage and death. Regulatory T cells, or Tregs, are a fundamental component of the T cell repertoire, being generated in the thymus under positive selection by self peptides Hsieh et al. (2004). The Treg repertoire is as diverse as conventional T cells Hsieh et al. (2004) and performs vital immune suppressive functions. Removal of Tregs, e.g. by (cell sorted) adoptive transfer experiments, causes a variety of autoimmune disorders in rodents, whilst many autoimmune diseases can be associated with a misregulation of Tregs, e.g. IPEX Sakaguchi (2004).

Under exposure to their specific antigen, conventional T cells are activated, leading to secretion of growth cytokines (predominantly interleukin 2, denoted IL-2), and expression of the interleukin 2 receptor which triggers cytokine driven proliferation. However, in the presence of active Tregs, the growth of conventional T cells is inhibited. Part of this growth inhibition is the inhibition of IL-2 secretion by T cells Shevach et al. (2001); Thornton and Shevach (1998). Further, most studies indicate that regulation is not T cell specific, i.e. Tregs inhibit all conventional T cells independent of their antigen specificity Thornton and Shevach (2000), although a different report suggests the contrary Tanchot et al. (2004). Tregs clearly function to limit the autoimmune responses with a delicate balance between appropriate immune activation and immune response suppression being achieved.

How such a balance is established and controlled is the central focus of the papers by Burroughs et al. (2006, 2008, 2011a,b). For a review see Pinto et al. (2010) and references within. We observe that T cell proliferation through cytokines already has a control structure: cytokine driven growth exhibits a quorum population size threshold de Boer and Hogeweg (1987). For low antigenic stimulation b of T cells, only one stable equilibria is found characterized by low concentrations of T cells, thus corresponding to an controlled state. For high antigenic stimulation b of T cells, again only one stable equilibria is found, this time corresponding to an immune response state, with high values of the concentration of T cells, close to the capacity of T cells. For intermediate values of the antigenic stimulation b of T cells, between two catastrophe points b_L and b_H, two stable equilibria are found, a controlled and an immune response state. Furthermore, an unstable equilibria is also present. If the antigenic stimulation rises above the threshold b_H, control is lost and autoimmunity arises. Note that even if the antigenic stimulation level b falls to the original value, at which control was originally achieved, control may not be reacquired. Control is only attained if stimulation falls below the second threshold b_L. This phenomena, termed hysteresis, is common in many physical and biological systems. Burroughs et al. (2006) propose that Tregs locally adjust these thresholds by inhibiting IL-2 secretion. The immune response-suppression axis is then a balance between the local numbers of activated T cells (e.g. from a pathogen encounter) and activated Tregs. Burroughs et al. (2011b) introduce an asymmetry reflecting that the difference between the growth and death rates can be higher for active T cells and active Tregs than for inactive T cells and inactive Tregs. This asymmetry can be explained by the effect of memory T cells. The memory T cells last longer than the other T cells and react more promptly to their specific antigen Rogers et al. (2000). This results in a positive correlation between the antigenic stimulation and the difference between the growth rate and the death rate of T cells. Hence, this asymmetry brings up the relevance of the antigenic stimulation of Tregs in the control of the local Treg population size, Burroughs et al. (2011b). Moreover, under homeostasis, a larger antigenic stimulation of Tregs results in a larger Treg population size. Furthermore, with this asymmetry, Burroughs et al. (2011b) observe a faster immune response and an improvement in the simulation of the bystander proliferation. Additionally, Burroughs et al. (2011b) found a positive correlation between the antigenic stimulation of Tregs and the thresholds b_L and b_H of antigenic stimulation of T cells. With it, by adjusting the level of self-antigenic stimulation of Tregs to different levels, organs can have different levels of protection against the development of an (auto-)immune response by T cells. Antigen presenting cells (APC), such as dendritic cells can stimulate both T cells and Tregs, León et al. (2003). We will study a relation between the antigenic stimulation a of Tregs and the antigenic stimulation b of T cells. For simplicity, we will analyse a linear tuning between

these stimuli as in Burroughs et al. (2011b), with the slope parameter modeling the effect of the antigen presenting cells (APC). Changing the slope parameter reveals the presence of an isola. Additionally, a transcritical bifurcation occurs when the isola merges with the hysteresis, Burroughs et al. (2011b). This transcritical bifurcation may give rise to two alternative scenarios, depending on the rate of increase of the antigenic stimuli: in one case the appearance of autoimmune responses (fast increase) and in another case the suppression of the immune responses (slow increase), Pinto et al. (2010).

This Thesis encompasses the results that we have obtained in this model. In Section 2.2, we present our immune response model as a set of five ordinary differential equations. In Section 2.3, we present approximate and exact formulas for the balance between the concentration of T cells and the concentration of Tregs, the antigen function that relates these two concentrations and the antigenic stimulation of T cells and the antigen function when we consider a tuning between the antigenic stimuli. We discuss the results in Section 2.4.

2.2 Theory

There are a number of different (CD4) T cell regulatory phenotypes reported; we use a model of Tregs that are currently identified as $CD25^+$ T cells, although this is not a definitive molecular marker. At a genetic level, these Tregs express Foxp3, a master regulator of the Treg phenotype inducing CD25, CTLA-4 and GITR expression, all correlating with a suppressive phenotype Sakaguchi (2004).

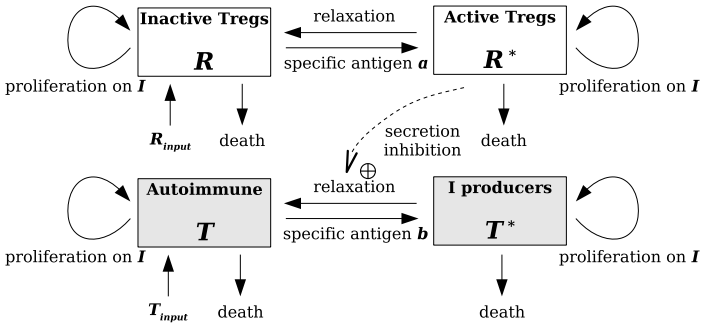

Figure 2.1: Model schematic showing growth, death and phenotype transitions of the Treg populations R, R^*, and autoimmune T cell T, T^* populations. Cytokine dynamics are not shown: IL-2 is secreted by activated T cells T^* and adsorbed by all the T cell populations. Reproduced from Burroughs et al. (2011b).

Our model from Burroughs et al. (2011b) uses a population of Tregs and conventional T cells with processes shown schematically in Figure 2.1. Both populations require antigenic stimulation for activation. Levels of antigenic stimulation are denoted a and b for Tregs and conventional T cells respectively. Tregs are activated by self antigens from an inactive state, denoted R, to an active state R^*. The IL-2 secreting T cells are denoted T^* and the non secreting T cells are denoted T. On activation conventional T cells secrete IL-2 and acquire proliferative capacity in the presence of IL-2. Tregs also proliferate in the presence of IL-2 although less efficiently than normal T cells Thornton and Shevach (1998), and they do not secrete IL-2. Finally, we include an influx of (auto) immune T cells into the tissue (T_{input}) and Tregs (R_{input}), which can represent T cell circulation or naive T cell input from the thymus.

The model consists of a set of ordinary differential equations. We have a compartment for each T cell population (inactive Tregs R, active Tregs R^*, non secreting T cells T, secreting activated T cells T^*) and interleukin 2 density I:

$$\frac{dR}{dt} = (\epsilon\rho I - \beta(R + R^* + T + T^*) - d_R)R + \hat{k}(R^* - aR) + R_{input}, \quad (2.1)$$

$$\frac{dR^*}{dt} = (\epsilon\rho I - \beta(R + R^* + T + T^*) - d_{R^*})R^* - \hat{k}(R^* - aR), \quad (2.2)$$

$$\frac{dT}{dt} = (\rho I - \beta(R + R^* + T + T^*) - d_T)T + k(T^* - bT + \gamma R^* T^*) + T_{input}, \quad (2.3)$$

$$\frac{dT^*}{dt} = (\rho I - \beta(R + R^* + T + T^*) - d_{T^*})T^* - k(T^* - bT + \gamma R^* T^*), \quad (2.4)$$

$$\frac{dI}{dt} = \sigma(T^* - (\alpha(R + R^* + T + T^*) + \delta)I). \quad (2.5)$$

The parameters of the model are in Table 2.1, adapted from Burroughs et al. (2006, 2011b); Figueiredo et al. (2014). The column value indicate the default values of the parameters used in the figures.

The model studied here keeps the basic properties of the immune response by T cells, controlled by Tregs, that were present in Burroughs et al. (2006, 2008). The main distinction of this model is the asymmetry in the difference between the growth and death rates modeled as in Burroughs et al. (2011a,b); Pinto et al. (2010). With this kind of asymmetry present for the T cells, an increase in the antigenic stimulation of T cells results in an increase in the population of T cells caused both by the increase in cytokine secretion and by the decrease in the average death rate of T cells. Furthermore, the asymmetry improves the dynamic behavior of the model, introduced in Burroughs et al. (2006), as shown previously in Burroughs et al. (2011a,b).

Parameter	Symbol	Range	Value
T cell T, T^*			
T cell Maximum growth rate[a]	ρ/α	< 6 day^{-1}	4 day^{-1}
Death rate of inactive T cells	d_T	$0.1 - 0.01$ day^{-1} Michie et al. (1992)	0.1 day^{-1}
Death rate ratio of active : inactive T cells	d_{T^*}/d_T	$0.01 - 100$	0.1
Capacity of T cells[b]	$\rho/(\alpha\beta)$	$10^6 - 10^7$ cells/ml Moskophidis et al. (1995)	10^7 cells/ml
Input rate of inactive T cells	T_{input}	$0 - 10^4$ cells/ml/day	0.100 cells/ml/day
Secretion reversion (constant)[c]	k	hrs-days	0.1 hr^{-1}
Antigen stimulation level	bk	$0.001 - 200 \times a\hat{k}$	Bifurcation parameter
Tregs R, R^*			
Growth rate ratio Tregs : T cells	ϵ	< 1	0.6
Homeostatic capacity	R_{hom}	$10 - 10^5$ cells/ml	1.4×10^3 cells/ml
Relaxation rate	$\hat{k}$	hrs-days	0.1 hr^{-1}
Death rate ratio of inactive Tregs : T cells	d_R/d_T	$0.01 - 100$	1
Death rate relative ratio of Tregs : T cells	$\frac{d_{R^*}}{d_R}/\frac{d_{T^*}}{d_T}$	$0.01 - 100$	1
Input rate ratio of inactive Tregs : inactive T	R_{input}/T_{input}	$0.01 - 100$	1
T_{reg} antigen stimulation level	$a\hat{k}$	$0 - 10$ day^{-1}	1 day^{-1}
Secretion inhibition[d]	γ	$0.1 - 100 \times R_{hom}^{-1}$	$10\ R_{hom}^{-1}$
Cytokines			
Max. cytokine concentration[e]	$1/\alpha$	$100 - 500$ pM	200 pM
IL-2 secretion rate	σ	[f] 0.07, 2 fgrms h^{-1} Veiga-Fernandes et al. (2000)	10^6 molecs s^{-1} cell^{-1}
Cytokine decay rate	$\sigma\delta$	hrs-days	1.5 hr $^{-1}$ Anderson and Sorenson (1994)

[a] Minimum duration of $\mathrm{SG_2M}$ phase $\alpha\rho^{-1} \approx 3hrs$.
[b] Maximum T cell density for severe infections (based on LCMV).
[c] This is in absence of Tregs.
[d] This is in terms of the homeostatic Treg level R_{hom}.
[e] This is taken as 20 times the receptor affinity (10pM Lowenthal and Greene (1987)).
[f] Naive and memory cells respectively. This corresponds to 3000-10^5 molecules per h, IL-2 mass 15-18 kDa.

Table 2.1: Parameters of the model.

2.3 Equilibria of the model

In a ODE model, the equilibria, stable or unstable, is the set of points where all the derivatives vanish. Let $x = T+T^*$ be the total concentration of T cells and $y = R+R^*$ be the total concentration of Tregs. When the system is at equilibrium we have that:

$$\sigma(T^* - (\alpha(x+y)+\delta)I) = 0 \ , \tag{2.6}$$

$$(\epsilon\rho I - \beta(x+y) - d_R)R + \hat{k}(R^* - aR) + R_{input} = 0 \ , \tag{2.7}$$

$$(\epsilon\rho I - \beta(x+y) - d_{R^*})R^* - \hat{k}(R^* - aR) = 0 \ , \tag{2.8}$$

$$(\rho I - \beta(x+y) - d_T)T + k(T^* - bT + \gamma R^* T^*) + T_{input} = 0 \ , \tag{2.9}$$

$$(\rho I - \beta(x+y) - d_{T^*})T^* - k(T^* - bT + \gamma R^* T^*) = 0. \tag{2.10}$$

Let $\Delta_T = d_T - d_{T^*}$ and $\theta = k(1+b) - \Delta_T$. When $\Delta_T \ll k$, the T, T^* balance is much faster than the T cell death rates. We can use this information to obtain an approximate expression of the relation between T^* and x.

Lemma 1. *When the system is at equilibrium (stable or unstable) and $\Delta_T \ll k$, the concentration of active T cells T^* is given approximately by*

$$T^* \approx \frac{kbx^2}{(\theta + k\gamma R^*)x + T_{input}} \ . \tag{2.11}$$

Remark: For the default values of the parameters, we observe that $\Delta_T = 0.09 \ll 2.4 = k$. We can observe in figure 2.2 that, for different values of y, the difference between the approximate value and the exact value of T^* is smaller than 1%.

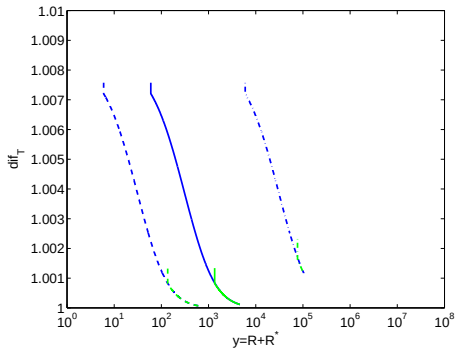

Figure 2.2: Relative deviation $dif_T = T^*_{approx}/T^*_{exact}$ between the approximate value of T^* obtained from the Lemma 1 and the exact value.
$T_{input} = 10$ (dashes), 100 (solid), and 10000 (dash-dot). The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

Proof of Lemma 1:

Adding (2.9) and (2.10), we obtain

$$\rho I - \beta(x+y) = \frac{d_T T + d_{T^*} T^* - T_{input}}{T + T^*} \ . \tag{2.12}$$

Subtracting (2.10) from (2.9), we get

$$\begin{aligned} &(\rho I - \beta(x+y))(T - T^*) - d_T T + d_{T^*} T^* \\ &+2k(T^* - bT + \gamma R^* T^*) + T_{input} = 0 \ . \end{aligned} \tag{2.13}$$

Replacing (2.12) in (2.13) we get

$$\begin{aligned} &\frac{T - T^*}{T + T^*}(d_T T + d_{T^*} T^* - T_{input}) - d_T T + d_{T^*} T^* \\ &+2k(T^* - bT + \gamma R^* T^*) + T_{input} = 0 \ . \end{aligned} \tag{2.14}$$

Since $T = x - T^*$, we have that $\frac{T-T^*}{T+T^*} = 1 - \frac{2T^*}{x}$ and we obtain,

$$\begin{aligned} &d_T(x - T^*) + d_{T^*} T^* - T_{input} - \frac{2T^*}{x}(d_T(x - T^*) + d_{T^*} T^* - T_{input}) \\ &-d_T(x - T^*) + d_{T^*} T^* \\ &+2k(T^* - b(x - T^*) + \gamma R^* T^*) + T_{input} = 0 \ . \end{aligned} \tag{2.15}$$

Multiplying equation (2.15) by $x/2$, reordering the terms and substituting $\Delta_T = d_T - d_{T^*}$ and $\theta = k(1+b) - \Delta_T$, we get

$$\Delta_T (T^*)^2 + \left((\theta + k\gamma R^*)\, x + T_{input}\right) T^* - kbx^2 = 0 \ . \tag{2.16}$$

We have a polynomial of the second degree in T^*. By using $H(x, R^*) = (\theta + k\gamma R^*)x + T_{input}$, we get

$$T^* = \frac{-H \pm \sqrt{H^2 + 4\Delta_T kbx^2}}{2\Delta_T} \ . \tag{2.17}$$

We must have $T^* > 0$, therefore we will only get the positive root. By assuming that $\Delta_T \ll k$, we can make a first order Taylor expansion of the square root around 1. Since $kb \lesssim \theta$ and $\Delta_T \ll \theta$, we have that

$$\Delta_T kbx^2 \lesssim \Delta_T \theta x^2 \ll \theta^2 x^2 < H^2 \ . \tag{2.18}$$

Therefore,

$$\sqrt{H^2 + 4\Delta_T kbx^2} = \sqrt{\left(1 + \frac{4\Delta_T kbx^2}{H^2}\right) H^2} \approx \left(1 + \frac{2\Delta_T kbx^2}{H^2}\right) H \ . \tag{2.19}$$

From (2.17) and (2.19) we get

$$T^* = \frac{-H + \left(1 + \frac{2\Delta_T kbx^2}{H^2}\right) H}{2\Delta_T} + \mathcal{O}(2) \ . \tag{2.20}$$

Simplifying this equation and using the expression of $H(x, R^*)$, we obtain (2.11).

□

2.3.1 Equilibria in the absence of the Tregs

We consider the simplified model of the immune response by T cells in the absence of Tregs, by assuming that $R = R^* = 0$, thus eliminating equations (2.7) and (2.8):

$$\begin{aligned}
\frac{dI}{dt} &= \sigma(T^* - (\alpha(T+T^*)+\delta)I), \\
\frac{dT}{dt} &= (\rho I - \beta(T+T^*) - d_T)T + k(T^* - bT) + T_{input}, \\
\frac{dT^*}{dt} &= (\rho I - \beta(T+T^*) - d_{T^*})T^* - k(T^* - bT).
\end{aligned}$$

Let

$$\begin{aligned}
\Delta_T &= d_T - d_{T^*} \\
E(x) &= (\alpha x + \delta)(d_T x - T_{input} + \beta x^2) \\
F(x) &= \rho x + \Delta_T(\alpha x + \delta)\ . \qquad (2.21)
\end{aligned}$$

Theorem 1. *Let $b_0(x)$ be the antigen function in the absence of Tregs. The level of antigenic stimulation of T cells is given approximately by $b_0(x)$, when the simplified system in the absence of Tregs is at equilibrium (stable or unstable).*

$$b_0(x) = \frac{\big((k-\Delta_T)x + T_{input}\big)E}{k\big(xF - E\big)x}\ . \qquad (2.22)$$

Conversely, given an antigenic stimulation level b_0 of T cells, the concentration x of T cells is a zero of a fourth order polynomial that can be explicitly constructed.

Proof of Theorem 1:

When the system is at equilibrium we have that:

$$\sigma(T^* - (\alpha x + \delta)I) = 0\ , \qquad (2.23)$$

$$(\rho I - \beta x - d_T)T + k(T^* - bT) + T_{input} = 0\ , \qquad (2.24)$$

$$(\rho I - \beta x - d_{T^*})T^* - k(T^* - bT) = 0. \qquad (2.25)$$

Solving (2.23) for T^* gives

$$T^* = I(\alpha x + \delta)\ . \qquad (2.26)$$

Adding (2.24) and (2.25), we obtain

$$(\rho I - \beta x - d_T)T + (\rho I - \beta x - d_{T^*})T^* + T_{input} = 0\ . \qquad (2.27)$$

Reordering the terms gives

$$(\rho I - \beta x)(T + T^*) - d_T T - d_{T^*}T^* + T_{input} = 0\ . \qquad (2.28)$$

Isolating $\rho I - \beta x$ we get

$$\rho I - \beta x = \frac{d_T T + d_{T^*} T^* - T_{input}}{T + T^*} \ . \tag{2.29}$$

Replacing (2.26) in (2.29) and using $T = x - T^*$ we get,

$$\left(\rho\left(\frac{T^*}{\alpha x + \delta}\right) - \beta x\right)(x - T^* + T^*) = d_T(x - T^*) + d_{T^*}T^* - T_{input} \ . \tag{2.30}$$

Using $\Delta_T = d_T - d_{T^*}$ we have,

$$\rho\left(\frac{T^*}{\alpha x + \delta}\right) x - \beta x^2 = d_T x - \Delta_T T^* - T_{input} \ . \tag{2.31}$$

Multiplying both sides by $\alpha x + \delta$

$$\rho x T^* - (\alpha x + \delta)\beta x^2 = (\alpha x + \delta)(d_T x - \Delta_T T^* - T_{input}) \ . \tag{2.32}$$

Isolating the terms with T^* gives

$$(\rho x + \Delta_T(\alpha x + \delta))T^* = (\alpha x + \delta)(d_T x - T_{input}) + (\alpha x + \delta)\beta x^2 \ . \tag{2.33}$$

Replacing $E(x) = (\alpha x + \delta)(d_T x - T_{input} + \beta x^2)$ and $F(x) = \rho x + \Delta_T(\alpha x + \delta)$, results in

$$T^* F = E \ . \tag{2.34}$$

Applying Lemma 1 for $R^* = 0$ we get,

$$\Big(\frac{kbx^2}{\theta x + T_{input}}\Big)F = E \ . \tag{2.35}$$

Since $\theta = k(1 + b) - \Delta_T = k + kb - \Delta_T$, we obtain

$$kbx^2 F = (k + kb - \Delta_T)xE + T_{input}E \ . \tag{2.36}$$

Moving the terms with b to the left side of the equation, we get

$$b(kx^2 F - xkE) = x(k - \Delta_T)E + T_{input}E \ . \tag{2.37}$$

By solving equation (2.37) for b we obtain (2.22).

□

Theorem 2. *Let $b_0(x)$ be the antigen function in the absence of Tregs. The level of antigenic stimulation of T cells is given exactly by $b_0(x)$, when the simplified system in the absence of Tregs is at equilibrium (stable or unstable).*

$$b_0(x) = \frac{\big(\Delta_T E + \big((k - \Delta_T)x + T_{input}\big)F\big)E}{k\big(xF - E\big)xF} \ . \tag{2.38}$$

Conversely, given an antigenic stimulation level b_0 of T cells, the concentration x of T cells is a zero of a sixth order polynomial that can be explicitly constructed.

Proof of Theorem 2:

We must take the positive root ($T^* > 0$) of equation (2.17) and replacing in (2.34).

$$\left(\frac{-H + \sqrt{H^2 + 4\Delta_T kbx^2}}{2\Delta_T}\right) F = E \ . \tag{2.39}$$

Multiplying by $2\Delta_T$ and isolating the square root

$$F\sqrt{H^2 + 4\Delta_T kbx^2} = 2\Delta_T E + FH \ . \tag{2.40}$$

Squaring both sides we have that

$$F^2H^2 + 4\Delta_T kbx^2F^2 = 4\Delta_T^2E^2 + 4\Delta_T EFH + F^2H^2 \ . \tag{2.41}$$

Simplifying the terms F^2H^2 and dividing both sides by $4\Delta_T$ gives

$$kbx^2F^2 = \Delta_T E^2 + EFH \ . \tag{2.42}$$

By using $H(x, R^*) = (\theta + k\gamma R^*)x + T_{input}$ and $R^* = 0$, we get

$$kbx^2F^2 = \Delta_T E^2 + (\theta x + T_{input})EF \ . \tag{2.43}$$

Since $\theta = k(1 + b) - \Delta_T = kb + k - \Delta_T$ we obtain

$$kbx^2F^2 = \Delta_T E^2 + (kbx + (k - \Delta_T)x + T_{input})\, EF \ . \tag{2.44}$$

Organizing the terms with b gives

$$k(xF - E)xFb = \big(\Delta_T E + ((k - \Delta_T)x + T_{input})\, F\big)E \ . \tag{2.45}$$

By solving equation (2.45) for b we obtain (2.38).

□

2.3.2 Equilibria in the presence of the Tregs

We now study the full model, with both T cells and Tregs. Let $\Delta_R = d_R - d_{R^*}$ and $\lambda = \hat{k}(1 + a) - \Delta_R$. Similarly to what is observed for the T cells, when $\Delta_R \ll \hat{k}$, the R, R^* balance is much faster than the Treg death rates. Once more, we can use this information to obtain an approximate expression of the relation between R^* and y.

Lemma 2. *When the system is at equilibrium (stable or unstable) and $\Delta_R \ll \hat{k}$, the concentration of active Tregs R^* is given approximately by*

$$R^* \approx \frac{\hat{k}ay^2}{\lambda y + R_{input}} \ . \tag{2.46}$$

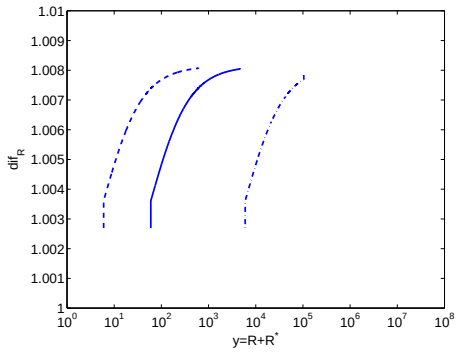

Figure 2.3: Relative deviation $dif_R = R^*_{approx}/R^*_{exact}$ between the approximate value of R^* obtained from the Lemma 2 and the exact value.
$T_{input} = 10$ (dashes), 100 (solid), and 10000 (dash-dot).

Remark: For the default values of the parameters, we observe that $\Delta_R = 0.09 \ll 2.4 = \hat{k}$. We can observe in figure 2.3 that, for different values of y, the relative difference between the approximate value and the exact value of R^* is smaller than 1%.

Proof of Lemma 2:

Adding (2.7) and (2.8), we obtain

$$\epsilon\rho I - \beta(x+y) = \frac{d_R R + d_{R^*} R^* - R_{input}}{R + R^*} \ . \tag{2.47}$$

Subtracting (2.8) from (2.7), we get

$$(\epsilon\rho I - \beta(x+y))(R - R^*) - d_R R + d_{R^*} R^* + 2\hat{k}(R^* - aR) + R_{input} = 0 \ . \tag{2.48}$$

Replacing (2.47) in (2.48) we get

$$\frac{R - R^*}{R + R^*}(d_R R + d_{R^*} R^* - R_{input}) - d_R R + d_{R^*} R^* + 2\hat{k}(R^* - aR) + R_{input} = 0 \ . \tag{2.49}$$

Since $R = y - R^*$, we have that $\frac{R-R^*}{R+R^*} = 1 - \frac{2R^*}{y}$. Hence we obtain,

$$\begin{aligned} &d_R(y - R^*) + d_{R^*} R^* - R_{input} - \frac{2R^*}{y}(d_R(y - R^*) + d_{R^*} R^* - R_{input}) - \\ &- d_R(y - R^*) + d_{R^*} R^* + 2\hat{k}(R^* - a(y - R^*)) + R_{input} = 0 \ . \end{aligned} \tag{2.50}$$

Multiplying equation (2.50) by $y/2$, reordering the terms and using $\lambda = \hat{k}(1 + a) - \Delta_R$, we obtain

$$\Delta_R (R^*)^2 + (\lambda y + R_{input})\, R^* - \hat{k} a y^2 = 0 \ . \tag{2.51}$$

The above is polynomial of the second degree in R^*. By substituting $L(y) = \lambda y + R_{input}$, we get

$$R^* = \frac{-L \pm \sqrt{L^2 + 4\Delta_R \hat{k} a y^2}}{2\Delta_R} \ . \tag{2.52}$$

We must have $R^* > 0$, therefore we will only get the positive root. By assuming that $\Delta_R \ll \hat{k}$, we can make a first order Taylor expansion of the square root around 1. Since $\hat{k}a \lesssim \lambda$ and $\Delta_R \ll \lambda$, we have that

$$\Delta_R \hat{k} a y^2 \lesssim \Delta_R \lambda y^2 \ll \lambda^2 y^2 < L^2 \ . \tag{2.53}$$

Therefore

$$\sqrt{L^2 + 4\Delta_R \hat{k} a y^2} = \sqrt{\left(1 + \frac{4\Delta_R \hat{k} a y^2}{L^2}\right) L^2} \approx \left(1 + \frac{2\Delta_R \hat{k} a y^2}{L^2}\right) L \ . \tag{2.54}$$

From (2.52) and (2.54) we get

$$R^* = \frac{-L + \left(1 + \frac{2\Delta_R \hat{k} a y^2}{L^2}\right) L}{2\Delta_R} + \mathcal{O}(2) \ . \tag{2.55}$$

Simplifying this equation and using the expression of $L(y)$ we obtain (2.46).

□

Using Lemma 2, we can obtain a polynomial that gives the balance between the concentration of T cells $x = T + T^*$ and the concentration of Tregs $y = R + R^*$ (see Figure 2.4). Let

$$\begin{aligned}
C(x,y) &= ((\epsilon d_T - d_R) - \beta(1-\epsilon)(x+y))\, xy \\
G(x,y) &= \rho x + \Delta_T(\alpha(x+y) + \delta) \\
L(y) &= \lambda y + R_{input} \\
P_{22} &= \beta\lambda\left(\alpha\Delta_T + \rho(1-\epsilon)\right) \\
P_{21} &= \beta R_{input}\left(\alpha\Delta_T + \rho(1-\epsilon)\right) \\
P_{13} &= \beta\lambda\left(2\alpha\Delta_T + \rho(1-\epsilon)\right) \\
P_{12} &= \beta R_{input}\left(2\alpha\Delta_T + \rho(1-\epsilon)\right) + \lambda\left(\rho(d_R - \epsilon d_T) + \Delta_T(\alpha d_R + \beta\delta)\right) - \hat{k}a\Delta_R(\rho + \alpha\Delta_T) \\
P_{11} &= R_{input}\big(\rho(d_R - \epsilon d_T) + \Delta_T(\alpha d_R + \beta\delta) - \lambda(\rho + \alpha\Delta_T)\big) \\
P_{10} &= -R_{input}^2\left(\rho + \alpha\Delta_T\right) \\
P_{04} &= \alpha\beta\lambda\Delta_T \\
P_{03} &= \Delta_T\left(\alpha\beta R_{input} + \lambda\left(\alpha d_R + \beta\delta\right) - \alpha\hat{k}a\Delta_R\right) \\
P_{02} &= \Delta_T R_{input}\left(\alpha d_R + \beta\delta\right) + \lambda\left(\epsilon\rho T_{input} - \alpha\Delta_T R_{input} + \delta\Delta_T d_R\right) - \delta\hat{k}a\Delta_T\Delta_R \\
P_{01} &= R_{input}\big(\epsilon\rho T_{input} - \alpha\Delta_T R_{input} + \delta\Delta_T(d_R - \lambda)\big) \\
P_{00} &= -\delta\Delta_T R_{input}^2 \ .
\end{aligned} \tag{2.56}$$

Theorem 3. *When the system is at equilibrium (stable or unstable) and $\Delta_R \ll \hat{k}$, the approximate concentration of T cells $x = T + T^*$ is given implicitly as function of the concentration of Tregs $y = R + R^*$ by the zeros of the second degree polynomial in x:*

$$P_{22}x^2y^2 + P_{21}x^2y + P_{13}xy^3 + P_{12}xy^2 + P_{11}xy + P_{10}x$$
$$+P_{04}y^4 + P_{03}y^3 + P_{02}y^2 + P_{01}y + P_{00} = 0 \ . \tag{2.57}$$

Conversely, the concentration y of Tregs is given implicitly as a function of the concentration x of T cells by the zeros of the above fourth order polynomial in y.

We observe that the the concentration y of Tregs is higher for values of the concentration x of T cells near $10^4 - 10^5$, see Figure 2.4.

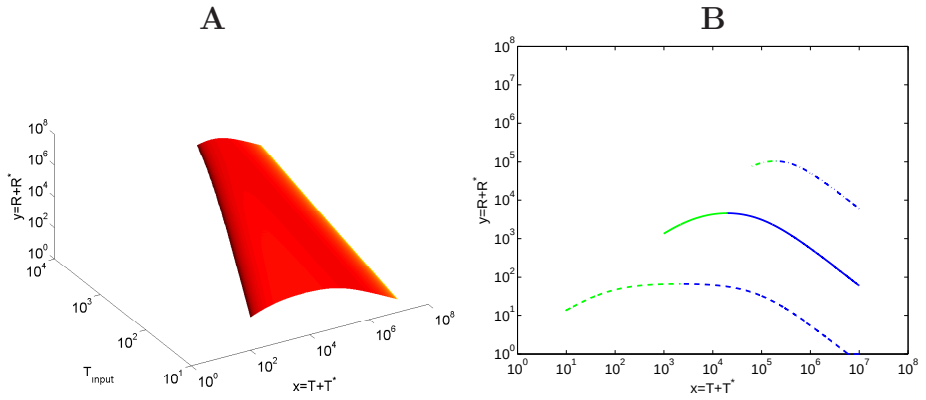

Figure 2.4: Relation between the concentration of T cells $x = T+T^*$, the concentration of Tregs $y = R + R^*$ and the relation T_{input}, from Theorem 3.
A: Horizontal axis: $x = T + T^*$; "away axis": T_{input}; vertical axis: $y = R + R^*$. Low values of b are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $T_{input} = 10$ (dashes), 100 (solid), and 10000 (dash-dot). The horizontal axis is the total concentration $x = T+T^*$ of T cells, and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

Proof of Theorem 3:

Isolating ρI from (2.12) gives:

$$\rho I = \frac{d_T T + d_{T^*} T^* - T_{input}}{T + T^*} + \beta(x + y) \ . \tag{2.58}$$

By replacing (2.58) in (2.12) we obtain

$$\epsilon \left(\frac{d_T T + d_{T^*} T^* - T_{input}}{T + T^*} + \beta(x + y) \right) - \beta(x + y) = \frac{d_R R + d_{R^*} R^* - R_{input}}{R + R^*} \ . \tag{2.59}$$

Since $T = x - T^*$ and $R = y - R^*$, and multiplying (2.59) by xy results in

$$\begin{aligned}&((\epsilon d_T - d_R) - \beta(1-\epsilon)(x+y))\, xy - \epsilon y\,((d_{T^*} - d_T)T^* - T_{input}) - \\ &-x\,((d_{R^*} - d_R)R^* - R_{input}) = 0\ .\end{aligned} \tag{2.60}$$

Using $C(x,y)$ from (2.56), $\Delta_T = d_T - d_{T^*}$ and $\Delta_R = d_R - d_{R^*}$ in (2.60) gives

$$C - \epsilon y\,(\Delta_T T^* + T_{input}) + x\,(\Delta_R R^* + R_{input}) = 0\ . \tag{2.61}$$

Multiplying (2.12) by x and using $T = x - T^*$, we obtain

$$\rho I x - \beta(x+y)x = d_T(x - T^*) + d_{T^*}T^* - T_{input}\ . \tag{2.62}$$

Reordering the terms of the previous expression and using $\Delta_T = d_T - d_{T^*}$ we have

$$\rho I x + \Delta_T T^* = \beta(x+y)x + d_T x - T_{input}\ . \tag{2.63}$$

Solving (2.6) for I we get

$$I = \frac{T^*}{\alpha(x+y) + \delta}\ . \tag{2.64}$$

Replacing (2.64) in (2.63) we get

$$\frac{\rho x}{\alpha(x+y)+\delta}T^* + \Delta_T T^* = \beta(x+y)x + d_T x - T_{input}\ . \tag{2.65}$$

Multiplying both sides of (2.65) by $\alpha(x+y)+\delta$ and solving for T^* we obtain

$$T^* = \frac{(\alpha(x+y)+\delta)\,(\beta(x+y)x + d_T x - T_{input})}{\rho x + \Delta_T(\alpha(x+y)+\delta)}\ . \tag{2.66}$$

Replacing (2.66) in (2.61), reordering the terms and using $G(x,y)$ from (2.56), we get

$$\begin{aligned}&C - \epsilon y\left(\Delta_T \frac{(\alpha(x+y)+\delta)\,(\beta(x+y)x + d_T x - T_{input})}{G} + T_{input}\right) + \\ &+x\,(\Delta_R R^* + R_{input}) = 0\ .\end{aligned} \tag{2.67}$$

Applying Lemma 2, using $L(y)$ from (2.56) and multiplying by $G(x,y)L(y)$ we have

$$\begin{aligned}&CGL - \epsilon y\big(\Delta_T(\alpha(x+y)+\delta)\,(\beta(x+y)x + d_T x - T_{input}) + T_{input}G\big)L + \\ &+x\left(\Delta_R \hat{k} a y^2 + R_{input}L\right)G = 0\ .\end{aligned} \tag{2.68}$$

Simplifying the previous expression, we obtain an implicit relation between the concentration of T cell $x = T + T^*$ and the concentration of Tregs $y = R + R^*$ given by (2.57). We note that $C(x,y)$, $G(x,y)$ and $L(y)$ are polynomials.

□

Theorem 4 presents a polynomial that gives the exact balance between the concentration of T cells $x = T+T^*$ and the concentration of Tregs $y = R+R^*$. Let $\Delta_R = d_R - d_{R^*}$, $\Delta_T = d_T - d_{T^*}$, $\lambda = \hat{k}(1+a) - \Delta_R$, $\theta = k(1+b) - \Delta_T$,

$$\begin{aligned} Z_1 &= \rho + \alpha\Delta_T \\ Z_2 &= \beta(1-\epsilon) \\ Z_3 &= \epsilon d_T - d_R \\ Z_4 &= (\lambda\delta - \alpha R_{input})\Delta_T \\ Z_5 &= \delta R_{input}\Delta_T \\ Z_6 &= \alpha\beta\Delta_T \\ Z_7 &= \alpha\lambda\Delta_T \\ Z_8 &= a\hat{k}\Delta_R\Delta_T \\ Z_9 &= (\alpha d_R + \beta\delta)\Delta_T \ , \end{aligned} \tag{2.69}$$

and let

$$\begin{aligned} N_1 &= Z_6 + \rho Z_2 \\ N_2 &= 2Z_6 + \rho Z_2 \\ N_3 &= Z_9 - \rho Z_3 \\ N_4 &= Z_6 \\ N_5 &= Z_9 \\ N_6 &= \alpha\Delta_T d_R + \rho\epsilon T_{input} \ . \end{aligned} \tag{2.70}$$

Let $W_{ij} = 0$ for all $0 \le i \le 4$ and $0 \le j \le 5$ except:

$$\begin{aligned} W_{41} &= N_1^2 \\ W_{32} &= 2N_1N_2 \\ W_{31} &= 2N_1N_3 + \lambda N_1Z_1 \\ W_{30} &= -\lambda R_{input}N_1Z_1 \\ W_{23} &= 2N_1N_4 + N_2^2 \\ W_{22} &= 2(N_1N_5 + N_2N_3) + N_1Z_7 + \lambda N_2Z_1 \\ W_{21} &= 2N_1N_6 + N_3^2 + N_1Z_4 - R_{input}N_2Z_1 + \lambda N_3Z_1 + a\hat{k}\Delta_R Z_1^2 \\ W_{20} &= -N_1Z_5 - R_{input}N_3Z_1 + \lambda R_{input}Z_1^2 \end{aligned}$$

$$
\begin{aligned}
W_{14} &= 2N_2N_4 \\
W_{13} &= 2(N_2N_5 + N_3N_4) + N_2Z_7 + \lambda N_4Z_1 \\
W_{12} &= 2(N_2N_6 + N_3N_5) + N_2Z_4 + N_3Z_7 - R_{input}N_4Z_1 + \lambda N_5Z_1 + 2\alpha Z_1Z_8 \\
W_{11} &= 2N_3N_6 - N_2Z_5 + N_3Z_4 - R_{input}N_5Z_1 + \lambda N_6Z_1 + 2(R_{input}Z_7 + \delta Z_8)Z_1 \\
W_{10} &= -N_3Z_5 - R_{input}N_6Z_1 + 2\lambda Z_1Z_5 \\
W_{05} &= N_4^2 \\
W_{04} &= 2N_4N_5 + N_4Z_7 \\
W_{03} &= 2N_4N_6 + N_5^2 + N_4Z_4 + N_5Z_7 + \alpha^2\Delta_T Z_8 \\
W_{02} &= 2N_5N_6 - N_4Z_5 + N_5Z_4 + N_6Z_7 + \alpha\Delta_T(2\delta Z_8 + R_{input}Z_7) \\
W_{01} &= N_6^2 - N_5Z_5 + N_6Z_4 + \delta\Delta_T(\delta Z_8 + 2R_{input}Z_7) \\
W_{00} &= -N_6Z_5 + \delta\lambda\Delta_T Z_5 \ . \qquad (2.71)
\end{aligned}
$$

Theorem 4. *Let W_{ij} be as above. When the system is at equilibrium (stable or unstable), the exact concentration of T cells $x = T + T^*$ is given implicitly as function of the concentration of Tregs $y = R + R^*$ by the zeros of the fourth order polynomial in x:*

$$\sum_{i=0}^{4}\sum_{j=0}^{5} W_{ij}x^i y^j = 0 \qquad (2.72)$$

Conversely, the exact concentration y of Tregs is given implicitly as a function of the concentration x of T cells by the zeros of the above fifth order polynomial in y.

Proof of Theorem 4:

Using $C(x, y)$ from (2.56) we can define

$$
\begin{aligned}
C_0(x, y) &= C - \epsilon y T_{input} \\
C_1(x, y) &= C_0 - \epsilon y \Delta_T T^* \ . \qquad (2.73)
\end{aligned}
$$

Applying $C_1(x, y)$ in (2.61) gives

$$C_1 + R_{input}x + \Delta_R x R^* = 0 \ . \qquad (2.74)$$

We must have $R^* > 0$. Thus, we take the positive root from (2.52). Replacing it in (2.74) we obtain

$$C_1 + R_{input}x + \Delta_R x\left(\frac{-L + \sqrt{L^2 + 4a\hat{k}\Delta_R y^2}}{2\Delta_R}\right) = 0 \ . \qquad (2.75)$$

Multiplying (2.75) by 2 and isolating the square root we get

$$2C_1 + 2R_{input}x - xL = -x\sqrt{L^2 + 4a\hat{k}\Delta_R y^2} \ . \qquad (2.76)$$

Squaring both sides of (2.76) we obtain

$$4C_1^2+8R_{input}xC_1-4xC_1L+4x^2R_{input}^2-4x^2R_{input}L+x^2L^2 = x^2L^2+4a\hat{k}\Delta_R x^2y^2 \ . \quad (2.77)$$

Simplifying the terms x^2L^2, dividing (2.77) by 4 and reorganizing the terms gives

$$C_1^2 + (2R_{input} - L)xC_1 + (R_{input} - L)R_{input}x^2 - a\hat{k}\Delta_R x^2y^2 = 0 \ . \quad (2.78)$$

Since $L(y) = \lambda y + R_{input}$,

$$C_1^2 + (R_{input} - \lambda y)xC_1 - \lambda R_{input}x^2y - a\hat{k}\Delta_R x^2y^2 = 0 \ . \quad (2.79)$$

Let

$$\begin{aligned} C_2(x,y) &= \alpha(x+y) + \delta \\ C_3(x,y) &= \beta(x+y)x \\ C_4(x,y) &= C_3 + d_T x - T_{input} \\ G(x,y) &= \rho x + \Delta_T C_2 \\ N(x,y) &= -C_1 G \\ U(x,y) &= (\lambda y - R_{input})x \\ V(x,y) &= a\hat{k}\Delta_R x^2y^2 + \lambda R_{input}x^2y \ . \end{aligned} \quad (2.80)$$

Multiplying equation (2.79) by $G^2(x,y)$ and using the definitions of $N(x,y)$, $U(x,y)$ and $V(x,y)$ we have

$$N^2 + GNU + G^2V = 0 \ . \quad (2.81)$$

In order to present the polynomial that equation (2.81) represents, we will start by computing $N(x,y)$. Applying (2.80), the formula for T^* in (2.66) becomes

$$T^* = \frac{C_2C_4}{G} \ . \quad (2.82)$$

Therefore, multiplying equation (2.73) by $-G(x,y)$ gives

$$N(x,y) = \epsilon\Delta_T y C_2C_4 - C_0G \ . \quad (2.83)$$

Applying the definitions of $C_0(x,y)$, $C_4(x,y)$ and $G(x,y)$

$$N(x,y) = \epsilon\Delta_T y C_2\big(C_3 + d_T x - T_{input}\big) - (C - \epsilon T_{input}y)(\rho x + \Delta_T C_2) \ . \quad (2.84)$$

Using (2.56) and the definitions of Z_3 from (2.69) we have

$$C(x,y) = Z_3xy - (1-\epsilon)yC_3 \ . \quad (2.85)$$

Applying in (2.84) we obtain

$$\begin{aligned} N(x,y) &= \epsilon\Delta_T y C_2\big(C_3 + d_T x - T_{input}\big) \\ &\quad -\big(Z_3xy - (1-\epsilon)yC_3 - \epsilon T_{input}y\big)(\rho x + \Delta_T C_2) \ . \end{aligned} \quad (2.86)$$

Expanding the products gives

$$\begin{aligned} N(x,y) &= \epsilon\Delta_T y C_2 C_3 + \epsilon\Delta_T d_T xy C_2 - \epsilon\Delta_T T_{input} y C_2 \\ &\quad -\rho Z_3 x^2 y + (1-\epsilon)\rho xy C_3 + \epsilon\rho T_{input} xy \\ &\quad -\Delta_T Z_3 xy C_2 + (1-\epsilon)\Delta_T y C_2 C_3 + \epsilon\Delta_T T_{input} y C_2 \ . \end{aligned} \tag{2.87}$$

Reordering the terms we have

$$\begin{aligned} N(x,y) &= \Delta_T(\epsilon + 1 - \epsilon) y C_2 C_3 + \Delta_T\big(\epsilon d_T x - \epsilon T_{input} - Z_3 x + \epsilon T_{input}\big) y C_2 \\ &\quad +(1-\epsilon)\rho x C_3 + \rho(\epsilon T_{input} - Z_3 x) xy \ . \end{aligned} \tag{2.88}$$

Simplifying and applying the definitions of Z_3, $C_2(x,y)$ and $C_3(x,y)$ gives

$$\begin{aligned} N(x,y) &= \Delta_T y(\alpha x + \alpha y + \delta)\beta(x+y)x + \Delta_T\big(\epsilon d_T x - (\epsilon d_T - d_R)x\big) y(\alpha x + \alpha y + \delta) \\ &\quad +(1-\epsilon)\rho xy\beta(x+y)x + \rho(\epsilon T_{input} - Z_3 x) xy \ . \end{aligned} \tag{2.89}$$

By expanding the products we obtain

$$\begin{aligned} N(x,y) &= \beta\Delta_T\big(\alpha(x^2 + 2xy + y^2) + \delta x + \delta y\big) xy + \Delta_T d_R(\alpha x^2 y + \alpha x y^2 + \delta xy) \\ &\quad +(1-\epsilon)\beta\rho(x^3 y + x^2 y^2) + \epsilon\rho T_{input} xy - \rho Z_3 x^2 y \ . \end{aligned} \tag{2.90}$$

Ordering the terms and using the definitions of Z_i from (2.69) gives

$$\begin{aligned} N(x,y) &= \big(Z_6 + \rho Z_2\big)x^3 y + \big(2Z_6 + \rho Z_2\big)x^2 y^2 \\ &\quad +\big(\delta\beta\Delta_T + \alpha\Delta_T d_R - \rho Z_3\big)x^2 y + Z_3 x y^3 \\ &\quad +Z_9 x y^2 + \big(\delta\Delta_T d_R + \epsilon\rho T_{input}\big) xy \ . \end{aligned} \tag{2.91}$$

Using the definitions of N_i from (2.70) we have that

$$N(x,y) = N_1 x^3 y + N_2 x^2 y^2 + N_3 x^2 y + N_4 x y^3 + N_5 x y^2 + N_6 xy \ . \tag{2.92}$$

Computing the product $N^2(x,y)$ yields:

$$\begin{aligned} N^2(x,y) &= N_1^2x^6y^2 \\ &\quad +2N_1N_2x^5y^3 \\ &\quad +2N_1N_3x^5y^2 \\ &\quad +\big(2N_1N_4+N_2^2\big)x^4y^4 \\ &\quad +2\big(N_1N_5+N_2N_3\big)x^4y^3 \\ &\quad +\big(2N_1N_6+N_3^2\big)x^4y^2 \\ &\quad +2N_2N_4x^3y^5 \\ &\quad +2\big(N_2N_5+N_3N_4\big)x^3y^4 \\ &\quad +2\big(N_2N_6+N_3N_5\big)x^3y^3 \\ &\quad +2N_3N_6x^3y^2 \\ &\quad +N_4^2x^2y^6 \\ &\quad +2N_4N_5x^2y^5 \\ &\quad +\big(2N_4N_6+N_5^2\big)x^2y^4 \\ &\quad +2N_5N_6x^2y^3 \\ &\quad +N_6^2x^2y^2\ . \end{aligned} \tag{2.93}$$

We will now obtain the polynomial of the second parcel of (2.81). Using the definition of $C_2(x,y)$ in $G(x,y)$ gives

$$G(x,y)=\rho x+\Delta_T(\alpha(x+y)+\delta)\ . \tag{2.94}$$

Applying the definition of Z_1 from (2.69), we obtain

$$G(x,y)=Z_1x+\alpha\Delta_Ty+\delta\Delta_T\ . \tag{2.95}$$

Using the definition of $U(x,y)$ from (2.80), we can compute the product $GU(x,y)$

$$\begin{aligned} GU(x,y) &= \lambda Z_1x^2y-R_{input}Z_1x^2+\alpha\lambda\Delta_Txy^2 \\ &\quad +\Delta_T(\delta\lambda-\alpha R_{input})xy-\delta\Delta_TR_{input}x\ . \end{aligned} \tag{2.96}$$

Using the definitions of Z_i from (2.69) we have that

$$GU(x,y)=\lambda Z_1x^2y-R_{input}Z_1x^2+Z_7xy^2+Z_4xy-Z_5x\ . \tag{2.97}$$

Multiplying the equation above by $N(x,y)$ gives

$$\begin{aligned} GNU(x,y) &= \lambda N_1 Z_1 x^5 y^2 - R_{input} N_1 Z_1 x^5 y \\ &+ N_1 Z_7 x^4 y^3 + N_1 Z_4 x^4 y^2 - N_1 Z_5 x^4 y \\ &+ \lambda N_2 Z_1 x^4 y^3 - R_{input} N_2 Z_1 x^4 y^2 + N_2 Z_7 x^3 y^4 \\ &+ N_2 Z_4 x^3 y^3 - N_2 Z_5 x^3 y^2 + \lambda N_3 Z_1 x^4 y^2 - R_{input} N_3 Z_1 x^4 y \\ &+ N_3 Z_7 x^3 y^3 + N_3 Z_4 x^3 y^2 - N_3 Z_5 x^3 y \\ &+ \lambda N_4 Z_1 x^3 y^4 - R_{input} N_4 Z_1 x^3 y^3 + N_4 Z_7 x^2 y^5 \\ &+ N_4 Z_4 x^2 y^4 - N_4 Z_5 x^2 y^3 + \lambda N_5 Z_1 x^3 y^3 \\ &- R_{input} N_5 Z_1 x^3 y^2 + N_5 Z_7 x^2 y^4 + N_5 Z_4 x^2 y^3 \\ &- N_5 Z_5 x^2 y^2 + \lambda N_6 Z_1 x^3 y^2 - R_{input} N_6 Z_1 x^3 y \\ &+ N_6 Z_7 x^2 y^3 + N_6 Z_4 x^2 y^2 - N_6 Z_5 x^2 y \ . \end{aligned} \tag{2.98}$$

Reorganizing the terms we obtain

$$\begin{aligned} GNU(x,y) &= \lambda N_1 Z_1 x^5 y^2 \\ &- R_{input} N_1 Z_1 x^5 y \\ &+ (N_1 Z_7 + \lambda N_2 Z_1) x^4 y^3 \\ &+ \big(N_1 Z_4 - R_{input} N_2 Z_1 + \lambda N_3 Z_1\big) x^4 y^2 \\ &- (N_1 Z_5 + R_{input} N_3 Z_1) x^4 y \\ &+ (N_2 Z_7 + \lambda N_4 Z_1) x^3 y^4 \\ &+ (N_2 Z_4 + N_3 Z_7 - R_{input} N_4 Z_1 + \lambda N_5 Z_1) x^3 y^3 \\ &+ (-N_2 Z_5 + N_3 Z_4 - R_{input} N_5 Z_1 + \lambda N_6 Z_1) x^3 y^2 \\ &- (N_3 Z_5 + R_{input} N_6 Z_1) x^3 y \\ &+ N_4 Z_7 x^2 y^5 \\ &+ (N_4 Z_4 + N_5 Z_7) x^2 y^4 \\ &+ (-N_4 Z_5 + N_5 Z_4 + N_6 Z_7) x^2 y^3 \\ &+ (-N_5 Z_5 + N_6 Z_4) x^2 y^2 \\ &- N_6 Z_5 x^2 y \ . \end{aligned} \tag{2.99}$$

Finally we will present the polynomial of the third parcel of (2.81). From (2.95) we can compute the product $G^2(x,y)$

$$G^2(x,y) = Z_1^2 x^2 + 2\alpha\Delta_T Z_1 xy + 2\delta\Delta_T Z_1 x + \alpha^2\Delta_T^2 y^2 + 2\alpha\delta\Delta_T^2 y + \delta^2\Delta_T^2 \ . \tag{2.100}$$

By using the definition of $V(x,y)$ from (2.80), we can multiply it with (2.100) to obtain

$G^2V(x,y)$.

$$\begin{aligned} G^2V(x,y) &= a\hat{k}\Delta_R Z_1^2 x^4y^2 + 2\alpha a\hat{k}\Delta_R\Delta_T Z_1 x^3y^3 \\ &+2\delta a\hat{k}\Delta_R\Delta_T Z_1 x^3y^2 + \alpha^2 a\hat{k}\Delta_R\Delta_T^2 x^2y^4 \\ &+2\alpha\delta a\hat{k}\Delta_R\Delta_T^2 x^2y^3 + \delta^2 a\hat{k}\Delta_R\Delta_T^2 x^2y^2 \\ &+\lambda R_{input} Z_1^2 x^4y + 2\alpha\lambda R_{input}\Delta_T Z_1 x^3y^2 \\ &+2\delta\lambda R_{input}\Delta_T Z_1 x^3y + \alpha^2\lambda R_{input}\Delta_T^2 x^2y^3 \\ &+2\alpha\delta\lambda R_{input}\Delta_T^2 x^2y^2 + \delta^2\lambda R_{input}\Delta_T^2 x^2y \ . \end{aligned} \tag{2.101}$$

Using the definitions of Z_i from (2.69) and ordering the terms we have that

$$\begin{aligned} G^2V(x,y) &= a\hat{k}\Delta_R Z_1^2 x^4y^2 \\ &+\lambda R_{input} Z_1^2 x^4y \\ &+2\alpha Z_1 Z_8 x^3y^3 \\ &+2Z_1\left(\delta Z_8 + R_{input} Z_7\right) x^3y^2 \\ &+2\lambda Z_1 Z_5 x^3y \\ &+\alpha^2\Delta_T Z_8 x^2y^4 \\ &+\alpha\Delta_T\left(2\delta Z_8 + R_{input} Z_7\right) x^2y^3 \\ &+\delta\Delta_T\left(\delta Z_8 + 2R_{input} Z_7\right) x^2y^2 \\ &+\delta\lambda\Delta_T Z_5 x^2y \ . \end{aligned} \tag{2.102}$$

We note that $N(x,y)$ is divisible by xy, $U(x,y)$ is divisible by x and $V(x,y)$ is divisible by x^2y. Therefore we can add equations (2.93), (2.99) and (2.102) to obtain $N^2 + GNU + G^2V = 0$ and divide the sum by x^2y to obtain (2.72).

□

From Theorem 3, we are able to build the *antigen function* that relates the concentration of T cells $x = T + T^*$ and the concentration of Tregs $y = R + R^*$ with the level of the antigenic stimulation of T cells b. Let

$$\begin{aligned} \lambda &= \hat{k}(1+a) - \Delta_R \\ \theta &= k(1+b) - \Delta_T \\ C(x,y) &= \left((\epsilon d_T - d_R) - \beta(1-\epsilon)(x+y)\right) xy \\ L(y) &= \lambda y + R_{input} \\ J(x,y) &= \epsilon\Delta_T kxyL \\ M(x,y) &= C - T_{input}\epsilon y + R_{input}x \\ M_1(x,y) &= ML + \Delta_R a\hat{k}xy^2 \\ Q(x,y) &= ak\hat{k}\gamma xy^2 + T_{input}L \ . \end{aligned} \tag{2.103}$$

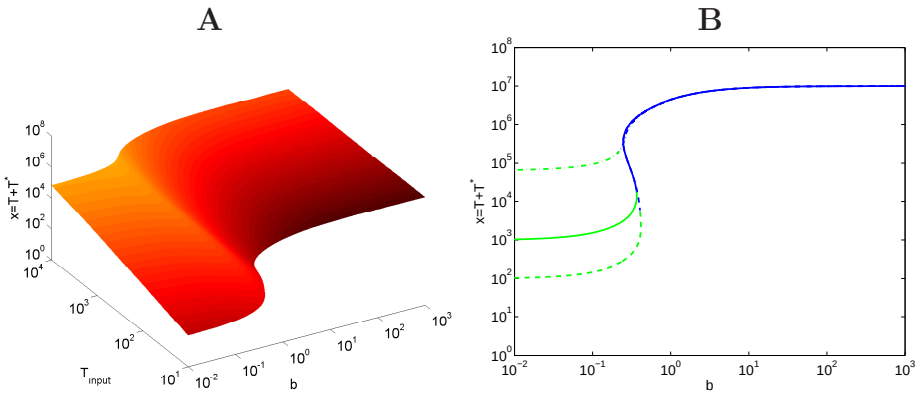

Figure 2.5: Relation between antigenic stimulation b of T cells, the concentration of T cells $x = T + T^*$ and the relation T_{input}.
A: Horizontal axis: b; "away axis": T_{input}; vertical axis: $x = T + T^*$. Low values of $y = R + R^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $T_{input} = 10$ (dashes), 100 (solid), and 10000 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells, and the vertical axis is the total concentration $x = T + T^*$ of T cells. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

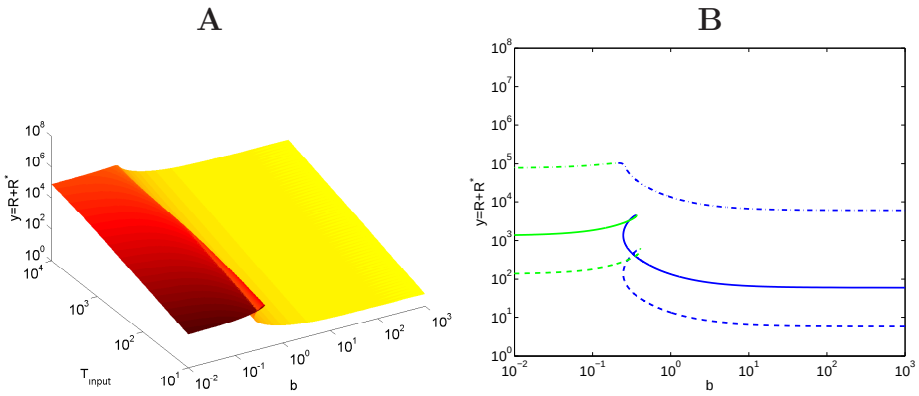

Figure 2.6: Relation between antigenic stimulation b of T cells, the concentration of Tregs $y = R + R^*$ and the relation T_{input}.
A: Horizontal axis: b; "away axis": T_{input}; vertical axis: $y = R + R^*$. Low values of $x = T + T^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $T_{input} = 10$ (dashes), 100 (solid), and 10000 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

Theorem 5. *Let $b(x,y)$ be the antigen function, and let $x(y)$ (or $y(x)$) be as in Theorem 3. The approximate level of the antigenic stimulation of T cells is given by $b(x,y)$, when the system is at equilibrium (stable or unstable).*

$$b(x,y) = \frac{\big((k-\Delta_T)Lx + Q\big)M_1}{\big(J - kM_1\big)Lx} \ . \tag{2.104}$$

Conversely, given an antigenic stimulation level b of T cells, the approximate concentration x of T cells and the approximate concentration y of Tregs are zeros of polynomials that can be explicitly constructed of degree three in x and degree five in y.

Proof of Theorem 5:

Isolating the T^* term in (2.61) gives

$$\epsilon\Delta_T y T^* = C - T_{input}\epsilon y + (\Delta_R R^* + R_{input})x \ . \tag{2.105}$$

Replacing T^* by the expression from Lemma 1, multiplying both sides of (2.105) by $(\theta + k\gamma R^*)x + T_{input}$ and using the definition of $M(x,y)$ from (2.103), results in

$$\epsilon\Delta_T kbx^2 y = (M + \Delta_R R^* x)\big((\theta + k\gamma R^*)x + T_{input}\big) \ . \tag{2.106}$$

Applying Lemma 2 to obtain an expression for R^* and multiplying both sides of (2.106) by $L^2(y)$ from (2.103), we get

$$\epsilon\Delta_T kbx^2 y L^2 = (ML + \Delta_R \hat{k}axy^2)\left((\theta L + k\gamma\hat{k}ay^2)x + T_{input}L\right) \ . \tag{2.107}$$

Using the definitions of $J(x,y)$, $M_1(x,y)$, $Q(x,y)$ and θ from (2.103), we obtain

$$bxJL = M_1\big((k(1+b) - \Delta_T)xL + Q\big) \ . \tag{2.108}$$

Moving the terms with b to the left side of the equation, we get

$$bxJL - bkxLM_1 = \big((k-\Delta_T)xL + Q\big)M_1 \ . \tag{2.109}$$

Solving the last expression for b gives us (2.104).

□

From Theorem 4, we are able to build the *antigen function* that relates exactly the concentration of T cells $x = T + T^*$ and the concentration of Tregs $y = R + R^*$ with

the level of the antigenic stimulation of T cells b. Let

$$\begin{aligned}
C(x,y) &= ((\epsilon d_T - d_R) - \beta(1-\epsilon)(x+y))\,xy \\
L(y) &= \lambda y + R_{input} \\
M(x,y) &= C - \epsilon T_{input} y + R_{input} x \\
D_0(x,y) &= M^2 + \epsilon(\theta x + T_{input})yM - \epsilon^2 k \Delta_T b x^2 y^2 \\
D_1(x,y) &= 2\Delta_R xM + \epsilon\gamma kxyM + \epsilon\Delta_R(\theta x + T_{input})xy \\
D_2(x,y) &= \big(\Delta_R + \epsilon\gamma k y\big)x^2 \\
D_3(y) &= 4a\hat{k}\Delta_R y^2 \\
D_4(x,y) &= \epsilon k x - \epsilon^2 k \Delta_T x^2 y^2 \\
D_5(x,y) &= 2M^2 + \epsilon((k-\Delta_T)x + T_{input})yM \\
D_6(x,y) &= \epsilon k \Delta_R x^2 y \\
D_7(x,y) &= (2\Delta_R + \epsilon\gamma k y)xM + \epsilon\Delta_R((k-\Delta_T)x + T_{input})xy\ , \qquad (2.110)
\end{aligned}$$

and

$$\begin{aligned}
A_1(x,y) &= -4D_3 \\
A_2(y) &= -16L \\
A_3 &= 16 \\
A_4(x,y) &= 4D_2D_3L \\
A_5(x,y) &= 8(2L^2 + D_3)D_2 \\
A_6(x,y) &= D_2^2 D_3^2\ . \qquad (2.111)
\end{aligned}$$

Let

$$\begin{aligned}
B_0(x,y) &= A_1D_7^2 + A_2D_5D_7 + A_3D_5^2 + A_4D_7 + A_5D_5 + A_6 \\
B_1(x,y) &= 2A_1D_6D_7 + A_2D_4D_7 + A_2D_5D_6 + 2A_3D_4D_5 + A_4D_6 + A_5D_4 \\
B_2(x,y) &= A_1D_6^2 + A_2D_4D_6 + A_3D_4^2\ . \qquad (2.112)
\end{aligned}$$

Theorem 6. *Let $B_0(x,y)$, $B_1(x,y)$ and $B_2(x,y)$ be defined as above. Let $b(x,y)$ be the antigen function, and let $x(y)$ (or $y(x)$) be as in Theorem 4. When the system is at equilibrium (stable or unstable), the exact level of the antigenic stimulation b of T cells is given by the zeros of:*

$$B_2b^2 + B_1b + B_0 = 0\ . \qquad (2.113)$$

Conversely, given an antigenic stimulation level b of T cells, the concentration x of T cells and the concentration y of Tregs are zeros of polynomials that can be explicitly constructed, of degree eight in x and y.

Proof of Theorem 6:

Using $M(x,y)$ from (2.110) in equation (2.61) we have

$$M + \Delta_R x R^* = \epsilon \Delta_T y T^* \ . \tag{2.114}$$

We must take the positive square root ($T^* > 0$) of (2.17), placing in (2.114),

$$M + \Delta_R x R^* = \epsilon \Delta_T y \Big(\frac{-H + \sqrt{H^2 + 4k\Delta_T b x^2}}{2\Delta_T} \Big) \ . \tag{2.115}$$

Multiplying by 2 and isolating the square root, we have that

$$2M + 2\Delta_R x R^* + \epsilon y H = \epsilon y \sqrt{H^2 + 4k\Delta_T b x^2} \ . \tag{2.116}$$

Squaring both terms gives

$$\begin{aligned} &4M^2 + 8\Delta_R x M R^* + 4\epsilon y H M + 4\Delta_R^2 x^2 R^{*2} \\ &+4\epsilon \Delta_R x y H M R^* + \epsilon^2 y^2 H^2 = \epsilon^2 y^2 (H^2 + 4k\Delta_T b x^2) \ . \end{aligned} \tag{2.117}$$

Simplifying the $\epsilon^2 y^2 H^2$ terms, dividing by 4 and using the definition of $H(x, R^*) = (\theta + \gamma k R^*)x + T_{input}$ we obtain

$$\begin{aligned} &M^2 + 2\Delta_R x M R^* + \epsilon y(\theta x + \gamma k x R^* + T_{input})M + \Delta_R^2 x^2 R^{*2} \\ &+\epsilon \Delta_R x y(\theta x + \gamma k x R^* + T_{input}) M R^* = \epsilon^2 k \Delta_T b x^2 y^2 \ . \end{aligned} \tag{2.118}$$

Reorganizing the terms as a polynomial in R^{*2} gives

$$\begin{aligned} &\Delta_R \big(\Delta_R + \epsilon \gamma k y \big) x^2 R^{*2} \\ &+ \big(2\Delta_R M + \epsilon \gamma k y M + \epsilon \Delta_R (\theta x + T_{input}) y \big) x R^* \\ &+ M^2 + \epsilon(\theta x + T_{input}) y M - \epsilon^2 k \Delta_T b x^2 y^2 = 0 \ . \end{aligned} \tag{2.119}$$

Using the definitions of D_i from (2.110) we have

$$\Delta_R D_2 R^{*2} + D_1 R^* + D_0 = 0 \ . \tag{2.120}$$

Since $\theta = k(1+b) - \Delta_T$, decomposing $D_0(x,y)$ from (2.110), to present the terms with b yields

$$D_0(x,y) \ = \ M^2 + \epsilon((k(1+b) - \Delta_T)x + T_{input}) y M - \epsilon^2 k \Delta_T b x^2 y^2 \ . \tag{2.121}$$

Isolating the terms in b,

$$D_0(x,y) \ = \ (\epsilon k x - \epsilon^2 k \Delta_T x^2 y^2) b + M^2 + \epsilon((k - \Delta_T)x + T_{input}) y M \ . \tag{2.122}$$

Using the definitions of $D_4(x,y)$ and $D_5(x,y)$ from (2.110) we can write

$$D_0(x,y) \ = \ D_4 b + D_5 \ . \tag{2.123}$$

For $D_1(x,y)$ we will also decompose it in terms with and without b:

$$\begin{aligned} D_1(x,y) &= (2\Delta_R + \epsilon\gamma k y)xM \\ &\quad +\epsilon\Delta_R((k(1+b)-\Delta_T)x + T_{input})xy \ . \end{aligned} \tag{2.124}$$

Again, isolating the terms in b we obtain

$$\begin{aligned} D_1(x,y) &= \epsilon k\Delta_R x^2 y b \\ &\quad +(2\Delta_R + \epsilon\gamma k y)xM + \epsilon\Delta_R((k-\Delta_T)x + T_{input})xy \ . \end{aligned} \tag{2.125}$$

Using the definitions of $D_6(x,y)$ and $D_7(x,y)$ from (2.110) we have

$$D_1(x,y) = D_6 b + D_7 \ . \tag{2.126}$$

The term $D_2(x,y)$ does not have any term with b. Applying the definition of $D_3(x,y)$ in the positive root ($R^* > 0$) of (2.52),

$$R^* = \frac{-L + \sqrt{L^2 + D_3}}{2\Delta_R} \ . \tag{2.127}$$

Using the expression above, we can compute $4\Delta_R^2 R^{*2}$, resulting in

$$\begin{aligned} 4\Delta_R^2 R^{*2} &= L^2 - 2L\sqrt{L^2+D_3} + L^2 + D_3 \\ &= 2L^2 + D_3 - 2L\sqrt{L^2+D_3} \ . \end{aligned} \tag{2.128}$$

Multiplying equation (2.120) by $4\Delta_R$ and using the formulas for R^* (2.127) and $4\Delta_R^2 R^{*2}$ (2.128) we have that

$$D_2\big(2L^2 + D_3 - 2L\sqrt{L^2+D_3}\big) + 2D_1(-L + \sqrt{L^2+D_3}) + 4D_0 = 0 \ . \tag{2.129}$$

Isolating the terms with the square root

$$(2L^2 + D_3)D_2 - 2LD_1 + 4D_0 = 2(D_2 L - D_1)\sqrt{L^2+D_3} \ . \tag{2.130}$$

Squaring both terms

$$\begin{aligned} &(2L^2+D_3)^2 D_2^2 - 4(2L^2+D_3)D_1 D_2 L \\ &+8(2L^2+D_3)D_0 D_2 + 4D_1^2 L^2 - 16 D_0 D_1 L + 16 D_0^2 \\ &= 4(D_2 L - D_1)^2 (L^2 + D_3) \ . \end{aligned} \tag{2.131}$$

Expanding the products we obtain

$$\begin{aligned} &(4L^4 + 4L^2 D_3 + D_3^2)D_2^2 - 4(2L^2+D_3)D_1 D_2 L \\ &+8(2L^2+D_3)D_0 D_2 + 4D_1^2 L^2 - 16 D_0 D_1 L + 16 D_0^2 \\ &= 4(D_2^2 L^2 - 2D_1 D_2 L + D_1^2)(L^2 + D_3) \ . \end{aligned} \tag{2.132}$$

We note that both sides have a term $4D_2^2L^2(L^2+D_3)$ and a term $4D_1^2L^2$. Simplifying them and organizing the terms in $D_0(x,y)$ and $D_1(x,y)$ we have

$$\begin{aligned}&-4D_3D_1^2\\&-16D_0D_1L\\&+16D_0^2\\&+4D_2D_3LD_1\\&+8(2L^2+D_3)D_2D_0\\&+D_2^2D_3^2=0\ .\end{aligned}\tag{2.133}$$

Using the definitions of A_i in (2.111) we can write

$$A_1D_1^2+A_2D_0D_1+A_3D_0^2+A_4D_1+A_5D_0+A_6=0\ .\tag{2.134}$$

Using (2.123) and (2.126), we have that

$$\begin{aligned}&A_1(D_6b+D_7)^2+A_2(D_4b+D_5)(D_6b+D_7)\\&+A_3(D_4b+D_5)^2+A_4(D_6b+D_7)\\&+A_5(D_4b+D_5)+A_6=0\ .\end{aligned}\tag{2.135}$$

Expanding the products,

$$\begin{aligned}&A_1(D_6^2b^2+2D_6D_7b+D_7^2)+A_2(D_4D_6b^2+D_4D_7b+D_5D_6b+D_5D_7)\\&+A_3(D_4^2b^2+2D_4D_5b+D_5^2)+A_4(D_6b+D_7)\\&+A_5(D_4b+D_5)+A_6=0\ .\end{aligned}\tag{2.136}$$

Organizing the terms as a quadratic polynomial in b gives

$$\begin{aligned}&\big(A_1D_6^2+A_2D_4D_6+A_3D_4^2\big)b^2\\&+\big(2A_1D_6D_7+A_2D_4D_7+A_2D_5D_6+2A_3D_4D_5+A_4D_6+A_5D_4\big)b\\&+A_1D_7^2+A_2D_5D_7+A_3D_5^2+A_4D_7+A_5D_5+A_6=0\ .\end{aligned}\tag{2.137}$$

Using the definitions of B_i from (2.112) we have equation (2.113).

□

2.3.3 Effect of the asymmetry parameters

For the default values of our parameters, the antigen function determines that the relation between the concentration x of T cells and the antigenic stimulation b of T cells is an hysteresis. The asymmetry affects the bistability region of the hysteresis, the

region bounded between the two catastrophe points b_L and b_H by moving the thresholds b_L and b_H, changing the distance between them and by merging them, resulting in a cusp bifurcation point, where the hysteresis unfolds. We also observe an effect in the concentration of Tregs when the parameters below are changed.

The hysteresis changes when we increase the relation $\frac{d_{T^*}}{d_T}$ between the death rates of active and inactive T cells. We observe a decrease in the concentration of Tregs when the relation $\frac{d_{T^*}}{d_T}$ increase (see Figure 2.7). Furthermore, the distance between the thresholds b_L and b_H reduces and for high values of $\frac{d_{T^*}}{d_T} \approx 0.977\ldots$ we observe the unfold of the hysteresis (see Figures 2.8 and 2.9).

A dramatic effect is observed when we increase the relation $\frac{d_R}{d_T}$ between the death rates of Tregs and T cells. The distance between the thresholds b_L and b_H is very large for low values of $\frac{d_R}{d_T}$. The concentration of Tregs is negatively correlated with $\frac{d_R}{d_T}$ (see Figure 2.10). When this relation is increased, the distance between b_L and b_H is reduced and the hysteresis is unfold for b_L and $\frac{d_R}{d_T} \approx 1.23\ldots$ (see Figures 2.11 and 2.12).

The concentration of Tregs are lower for large values of this parameter (see Figure 2.13). Higher values of the ratio $\frac{d_{R^*}}{d_R}/\frac{d_{T^*}}{d_T}$ between the death rates of active and inactive Tregs and active and inactive T cells give smaller distances between the thresholds b_L and b_H and an unfold of the hysteresis arises for $\frac{d_{R^*}}{d_R}/\frac{d_{T^*}}{d_T} \approx 7.94\ldots$ (see Figures 2.14 and 2.15).

The concentration of Tregs visibly decreases when $\frac{R_{input}}{T_{input}}$ is decreased (see Figure 2.16). When we decrease towards 0.1, the relation $\frac{R_{input}}{T_{input}}$ between the input Tregs and the input T cells, the hysteresis shrinks but does not unfold (see Figure 2.17). Nevertheless, for $\frac{R_{input}}{T_{input}} \approx 0.398\ldots$ the loop in the concentration y of Tregs observed for higher values of $\frac{R_{input}}{T_{input}}$ vanishes (see Figure 2.18).

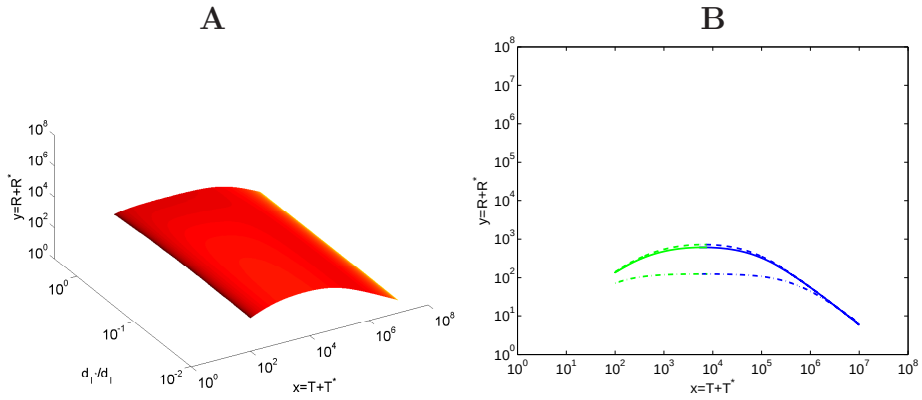

Figure 2.7: Relation between the concentration of T cells $x = T+T^*$, the concentration of Tregs $y = R + R^*$ and the relation $\frac{d_{T^*}}{d_T}$.
A: Horizontal axis: $x = T + T^*$; "away axis": $\frac{d_{T^*}}{d_T}$; vertical axis: $y = R + R^*$. Low values of b are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_{T^*}}{d_T} = 0.01$ (dashes), 0.1 (solid), and 2.5 (dash-dot). The horizontal axis is the total concentration $x = T + T^*$ of T cells, and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

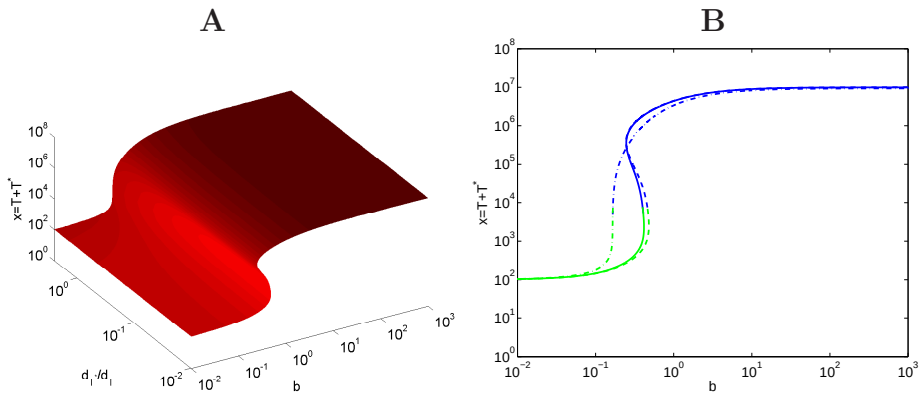

Figure 2.8: Relation between antigenic stimulation b of T cells, the concentration of T cells $x = T + T^*$ and the relation $\frac{d_{T^*}}{d_T}$.
A: Horizontal axis: b; "away axis": $\frac{d_{T^*}}{d_T}$; vertical axis: $x = T + T^*$. Low values of $y = R + R^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_{T^*}}{d_T} = 0.01$ (dashes), 0.1 (solid), and 2.5 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells, and the vertical axis is the total concentration $x = T + T^*$ of T cells. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

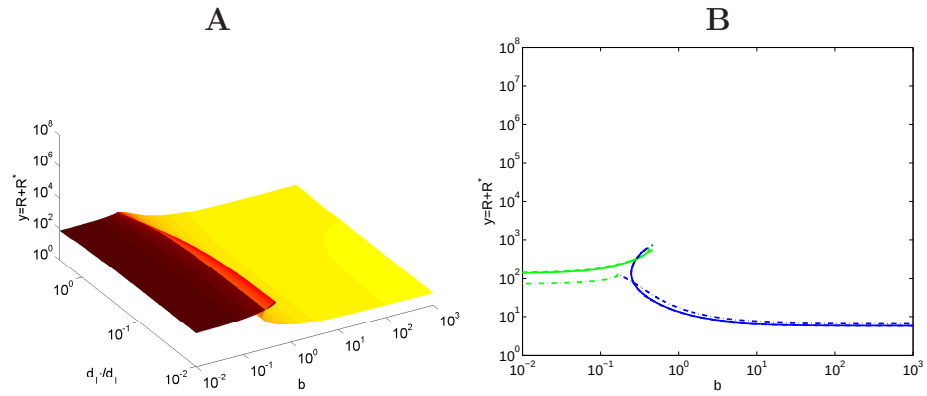

Figure 2.9: Relation between antigenic stimulation b of T cells, the concentration of Tregs $y = R + R^*$ and the relation $\frac{d_{T^*}}{d_T}$.
A: Horizontal axis: b; "away axis": $\frac{d_{T^*}}{d_T}$; vertical axis: $y = R + R^*$. Low values of $x = T + T^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_{T^*}}{d_T} = 0.01$ (dashes), 0.1 (solid), and 2.5 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells and the vertical axis is the total concentration $y = R+R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

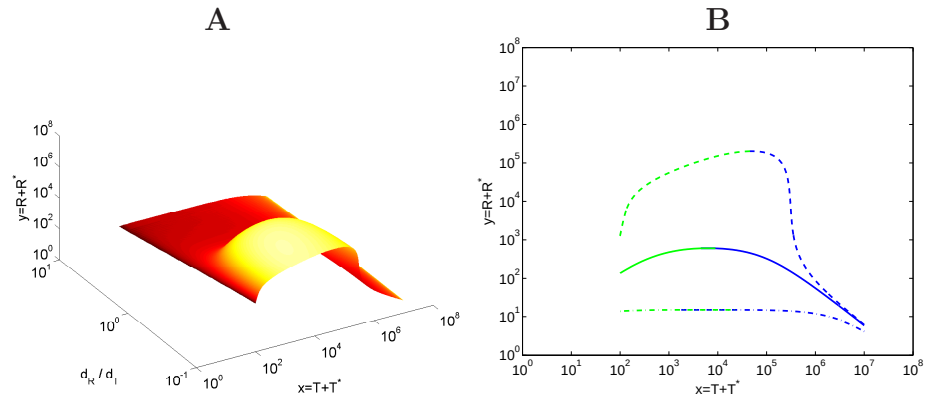

Figure 2.10: Relation between the concentration of T cells $x = T+T^*$, the concentration of Tregs $y = R + R^*$ and the relation $\frac{d_R}{d_T}$.
A: Horizontal axis: $x = T + T^*$; "away axis": $\frac{d_R}{d_T}$; vertical axis: $y = R + R^*$. Low values of b are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_R}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the total concentration $x = T + T^*$ of T cells, and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

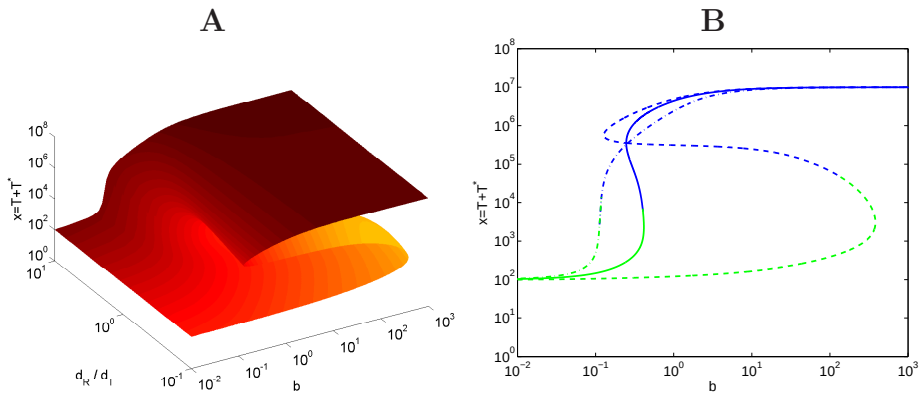

Figure 2.11: Relation between antigenic stimulation b of T cells, the concentration of T cells $x = T + T^*$ and the relation $\frac{d_R}{d_T}$.
A: Horizontal axis: b; "away axis": $\frac{d_R}{d_T}$; vertical axis: $x = T + T^*$. Low values of $y = R + R^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_R}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells, and the vertical axis is the total concentration $x = T + T^*$ of T cells. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

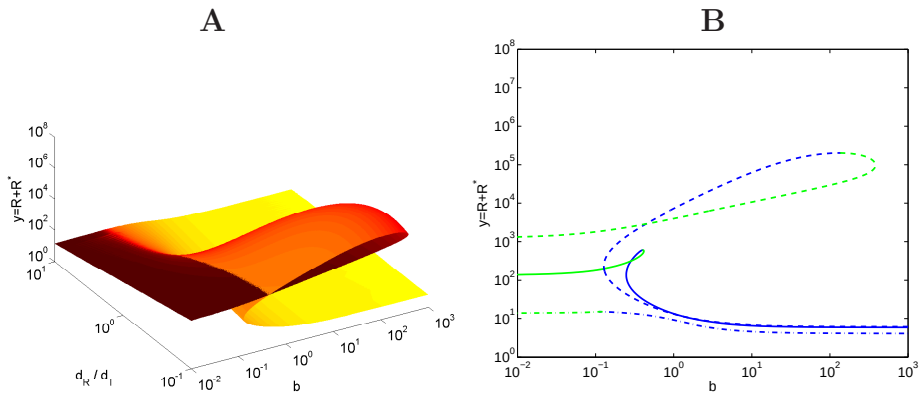

Figure 2.12: Relation between antigenic stimulation b of T cells, the concentration of Tregs $y = R + R^*$ and the relation $\frac{d_R}{d_T}$.
A: Horizontal axis: b; "away axis": $\frac{d_R}{d_T}$; vertical axis: $y = R + R^*$. Low values of $x = T + T^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_R}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

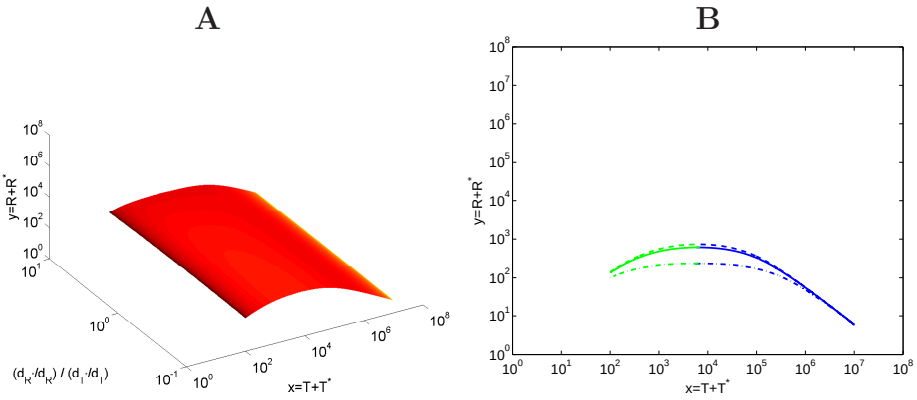

Figure 2.13: Relation between the concentration of T cells $x = T+T^*$, the concentration of Tregs $y = R + R^*$ and the relation $\frac{d_{R^*}}{d_R}/\frac{d_{T^*}}{d_T}$.
A: Horizontal axis: $x = T + T^*$; "away axis": $\frac{d_{R^*}}{d_R}/\frac{d_{T^*}}{d_T}$; vertical axis: $y = R + R^*$. Low values of b are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_{R^*}}{d_R}/\frac{d_T^*}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the total concentration $x = T + T^*$ of T cells, and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

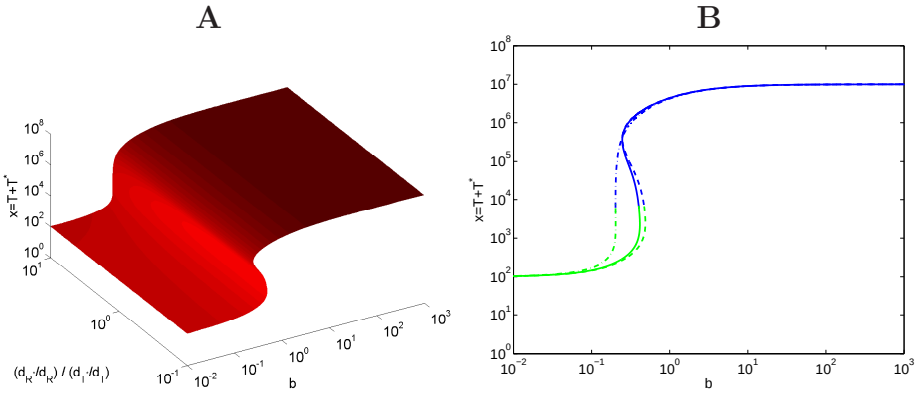

Figure 2.14: Relation between antigenic stimulation b of T cells, the concentration of T cells $x = T + T^*$ and the relation $\frac{d_{R^*}}{d_R}/\frac{d_{T^*}}{d_T}$.
A: Horizontal axis: b; "away axis": $\frac{d_{R^*}}{d_R}/\frac{d_{T^*}}{d_T}$; vertical axis: $x = T + T^*$. Low values of $y = R + R^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_{R^*}}{d_R}/\frac{d_T^*}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells, and the vertical axis is the total concentration $x = T + T^*$ of T cells. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

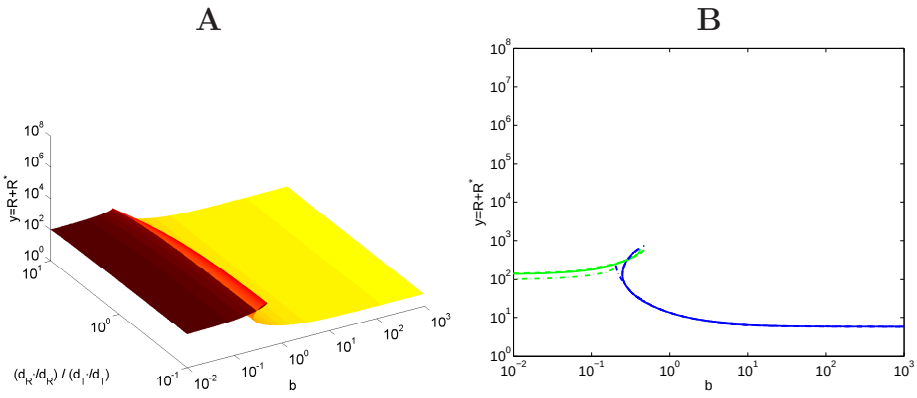

Figure 2.15: Relation between antigenic stimulation b of T cells, the concentration of Tregs $y = R + R^*$ and the relation $\frac{d_{R^*}}{d_R} / \frac{d_{T^*}}{d_T}$.
A: Horizontal axis: b; "away axis": $\frac{d_{R^*}}{d_R} / \frac{d_{T^*}}{d_T}$; vertical axis: $y = R + R^*$. Low values of $x = T + T^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{d_{R^*}}{d_R} / \frac{d_{T^*}}{d_T} = 0.1$ (dashes), 1 (solid), and 10 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

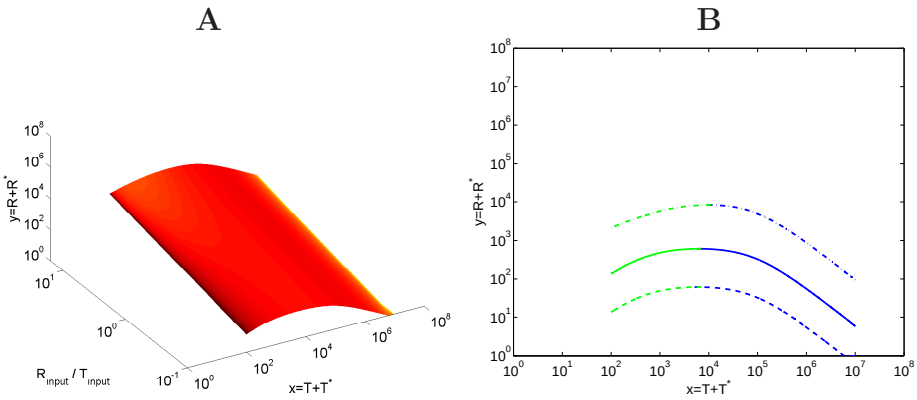

Figure 2.16: Relation between the concentration of T cells $x = T + T^*$, the concentration of Tregs $y = R + R^*$ and the relation $\frac{R_{input}}{T_{input}}$.
A: Horizontal axis: $x = T + T^*$; "away axis": $\frac{R_{input}}{T_{input}}$; vertical axis: $y = R + R^*$. Low values of b are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{R_{input}}{T_{input}} = 0.1$ (dashes), 1 (solid), and 16 (dash-dot). The horizontal axis is the total concentration $x = T + T^*$ of T cells, and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

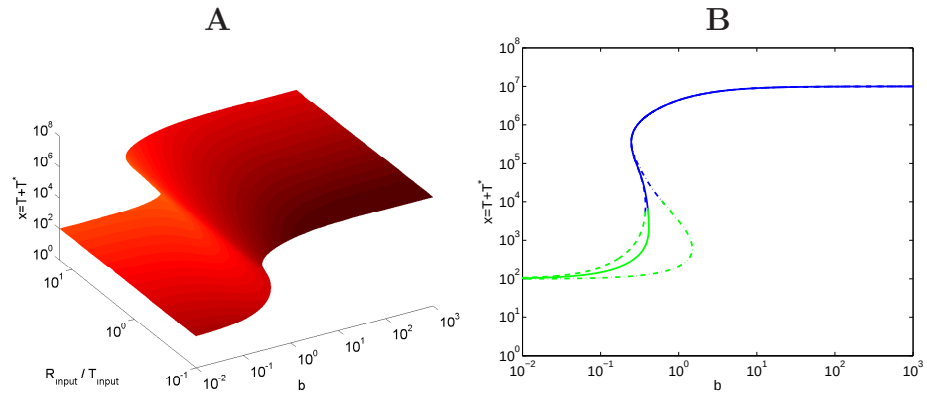

Figure 2.17: Relation between the antigenic stimulation b of T cells, the concentration of T cells $x = T + T^*$ and the relation $\frac{R_{input}}{T_{input}}$.
A: Horizontal axis: b; "away axis": $\frac{R_{input}}{T_{input}}$; vertical axis: $x = T + T^*$. Low values of $y = R + R^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{R_{input}}{T_{input}} = 0.1$ (dashes), 1 (solid), and 16 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells, and the vertical axis is the total concentration $x = T + T^*$ of T cells. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

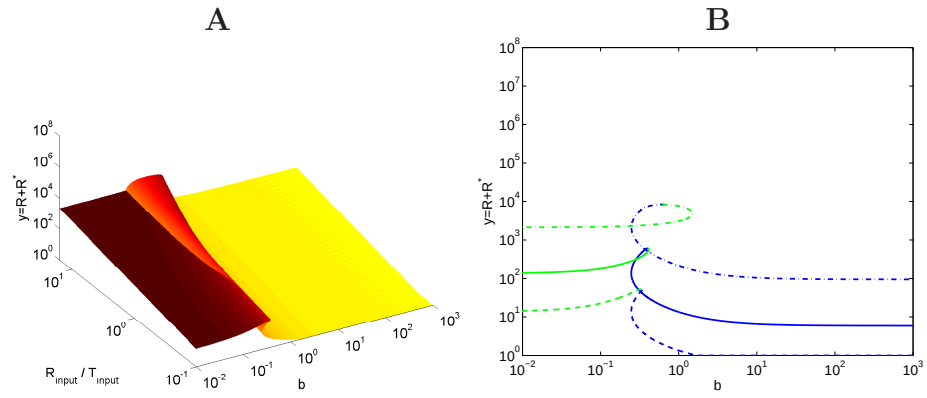

Figure 2.18: Relation between antigenic stimulation b of T cells, the concentration of Tregs $y = R + R^*$ and the relation $\frac{R_{input}}{T_{input}}$.
A: Horizontal axis: b; "away axis": $\frac{R_{input}}{T_{input}}$; vertical axis: $y = R + R^*$. Low values of $x = T + T^*$ are darker and higher values are lighter.
B: Cross sections of the equilibria manifold in figure A for $\frac{R_{input}}{T_{input}} = 0.1$ (dashes), 1 (solid), and 16 (dash-dot). The horizontal axis is the antigenic stimulation b of T cells and the vertical axis is the total concentration $y = R + R^*$ of Tregs. The colors indicate when it is plotted the smallest root (green) or largest root (blue) of x from Theorem 3.

2.3.4 Tuning between the antigenic stimuli

The antigen presenting cells (APC), such as dendritic cells, present both self and non self antigens León et al. (2004). Therefore, there is a positive correlation between the levels of antigen stimulation a of the Tregs and the levels of antigen stimulation $\hat{b}$ of the T cells. For simplicity, we study a linear tuning between these stimuli in the form:

$$a(\hat{b}) = a_0 + m\hat{b}, \tag{2.138}$$

with a_0 as in Burroughs et al. (2011b) and $m \geq 0$. If the levels of antigenic stimulation a of Tregs and the levels of antigen stimulation $\hat{b}$ of the T cells are independent, the slope m is equal to zero.

Using this linear tuning, we can expand the result from Theorem 5. Let

$$\begin{aligned}
\hat{\lambda} &= \hat{k}(1+a_0) - \Delta_R \\
\lambda(\hat{b}) &= \hat{\lambda} + \hat{k}m\hat{b} \\
C(x,y) &= ((\epsilon d_T - d_R) - \beta(1-\epsilon)(x+y))\, xy \\
\hat{L}(y) &= \hat{\lambda}y + R_{input} \\
\tilde{L}(y) &= \hat{k}my \\
L(y,\hat{b}) &= \hat{L} + \tilde{L}\hat{b} \\
\hat{J}(x,y) &= \epsilon\Delta_T kxy\hat{L} \\
\tilde{J}(x,y) &= \epsilon\Delta_T k\hat{k}mxy^2 \\
J(x,y,\hat{b}) &= \hat{J} + \tilde{J}\hat{b} \\
M(x,y) &= C - T_{input}\epsilon y + R_{input}x \\
\hat{M}_1(x,y) &= M\hat{L} + \Delta_R a_0 \hat{k}xy^2 \\
\tilde{M}_1(x,y) &= (M + \Delta_R xy)\,\hat{k}my \\
M_1(x,y,\hat{b}) &= \hat{M}_1 + \tilde{M}_1\hat{b} \\
M_2(x) &= (k - \Delta_T)x \\
\hat{Q}(x,y) &= a_0 k\hat{k}\gamma xy^2 + T_{input}\hat{L} \\
\tilde{Q}(x,y) &= (k\gamma xy + T_{input})\,\hat{k}my \\
Q(x,y) &= \hat{Q} + \tilde{Q}\hat{b} \\
Q_0(x,y) &= (M_2\hat{L} + \hat{Q})\hat{M}_1 \\
Q_1(x,y) &= (\hat{J} - k\hat{M}_1)x\hat{L} - ((M_2\hat{L} + \hat{Q})\tilde{M}_1 + (M_2\tilde{L} + \tilde{Q})\hat{M}_1) \\
Q_2(x,y) &= ((\hat{J} - k\hat{M}_1)\tilde{L} + (\tilde{J} - k\tilde{M}_1)\hat{L})x - (M_2\tilde{L} + \tilde{Q})\tilde{M}_1 \\
Q_3(x,y) &= (\tilde{J} - k\tilde{M}_1)x\tilde{L}\ .
\end{aligned} \tag{2.139}$$

Theorem 7. *Let $\hat{b}(x,y)$ be the tuned antigen function, let $a(\hat{b}) = a_0 + m\hat{b}$ and let $x(y)$ (or $y(x)$) be as in Theorem 3. The approximate level of antigenic stimulation $\hat{b}$ of T cells is a zero of the third degree polynomial $\hat{b}(x,y)$, when the system is at equilibrium (stable or unstable).*

$$Q_3\hat{b}^3 + Q_2\hat{b}^2 + Q_1\hat{b} + Q_0 = 0 \ . \tag{2.140}$$

Conversely, given an antigenic stimulation level $\hat{b}$ of T cells, the approximate concentration x of T cells and the approximate concentration y of Tregs are zeros of polynomials that can be explicitly constructed of degree three in x and degree five in y.

Note that Theorem 5 can be obtained as a corollary of Theorem 7 by assuming that the antigenic stimuli a and $\hat{b}$ are independent, i.e. by setting $m = 0$.

Proof of Theorem 7:

The equalities in (2.139) are obtained by applying (2.138) to equations (2.103). From equation (2.109), using the definition of $M_2(x)$ we have that

$$(J - kM_1)xL\hat{b} \ = \ (M_2L + Q)M_1 \ . \tag{2.141}$$

Replacing the definitions in (2.139) on the equation above we obtain

$$\begin{aligned} &(\hat{J} + \tilde{J}\hat{b} - k(\hat{M}_1 + \tilde{M}_1\hat{b}))x(\hat{L} + \tilde{L}\hat{b})\hat{b} \\ &= (M_2(\hat{L} + \tilde{L}\hat{b}) + (\hat{Q} + \tilde{Q}\hat{b}))(\hat{M}_1 + \tilde{M}_1\hat{b}) \ . \end{aligned} \tag{2.142}$$

Expanding the products to obtain polynomials in $\hat{b}$, we get

$$\begin{aligned} &(\tilde{J} - k\tilde{M}_1)x\tilde{L}\hat{b}^3 \\ &+((\hat{J} - k\hat{M}_1)\tilde{L} + (\tilde{J} - k\tilde{M}_1)\hat{L})x\hat{b}^2 \\ &+(\hat{J} - k\hat{M}_1)x\hat{L}\hat{b} \\ &= (M_2\tilde{L} + \tilde{Q})\tilde{M}_1\hat{b}^2 \\ &+((M_2\hat{L} + \hat{Q})\tilde{M}_1 + (M_2\tilde{L} + \tilde{Q})\hat{M}_1)\hat{b} \\ &+(M_2\hat{L} + \hat{Q})\hat{M}_1 \ . \end{aligned} \tag{2.143}$$

Reordering the terms of the previous expression and using the definitions of $Q_i(x,y)$ we obtain (2.140).

□

We are also able to obtain exact result when considering the tuning in (2.138). Let

$$\begin{aligned}
\hat{B}_0(x,y) &= A_1D_7^2 - 16D_5D_7L + A_3D_5^2 + 4D_2D_3D_7\hat{L} + A_5D_5 + A_6 \\
\tilde{B}_0(x,y) &= -16\hat{k}myD_5D_7 + 4\hat{k}myD_2D_3D_7 \\
\hat{B}_1(x,y) &= 2A_1D_6D_7 - 16(D_4D_7 + D_5D_6)\hat{L} \\
&\quad +2A_3D_4D_5 + 4D_2D_3D_6\hat{L} + A_5D_4 \\
\tilde{B}_1(x,y) &= -16\hat{k}my(D_4D_7 + D_5D_6) + \hat{k}myD_2D_3D_6 \\
\hat{B}_2(x,y) &= A_1D_6^2 - 16D_4D_6\hat{L} + A_3D_4^2 \\
\tilde{B}_2(x,y) &= -16\hat{k}myD_4D_6 \ . \qquad (2.144)
\end{aligned}$$

Theorem 8. *Let $\hat{b}(x,y)$ be the tuned antigen function, let $a(\hat{b}) = a_0 + m\hat{b}$ and let $x(y)$ (or $y(x)$) be as in Theorem 4. The exact level of antigenic stimulation $\hat{b}$ of T cells is a zero of the third degree polynomial $\hat{b}(x,y)$, when the system is at equilibrium (stable or unstable).*

$$\tilde{B}_2\hat{b}^3 + (\hat{B}_2 + \tilde{B}_1)\hat{b}^2 + (\hat{B}_1 + \tilde{B}_0)\hat{b} + \hat{B}_0 = 0 \ . \qquad (2.145)$$

Conversely, given an antigenic stimulation level $\hat{b}$ of T cells, the exact concentration x of T cells and the exact concentration y of Tregs are zeros of polynomials of degree eight in x and y that can be explicitly constructed.

Note that Theorem 6 can be obtained as a corollary of Theorem 8 by assuming that the antigenic stimuli a and $\hat{b}$ are independent, i.e. by setting $m = 0$.

Proof of Theorem 8:

In (2.111) the only terms that contain a are

$$\begin{aligned}
A_2(y) &= -16L \\
A_4(x,y) &= 4D_2D_3L \ . \qquad (2.146)
\end{aligned}$$

Hence, replacing these in $B_i(x,y)$, from equations (2.112), we have that

$$\begin{aligned}
B_0(x,y) &= A_1D_7^2 - 16D_5D_7L + A_3D_5^2 + 4D_2D_3D_7L + A_5D_5 + A_6 \\
B_1(x,y) &= 2A_1D_6D_7 - 16(D_4D_7 + D_5D_6)L \\
&\quad +2A_3D_4D_5 + 4D_2D_3D_6L + A_5D_4 \\
B_2(x,y) &= A_1D_6^2 - 16D_4D_6L + A_3D_4^2 \ . \qquad (2.147)
\end{aligned}$$

Using the definition of $L(y)$ from (2.139) and the formulas for $\hat{B}_i(x,y)$ and $\tilde{B}_i(x,y)$ from (2.144), we get

$$\begin{aligned}
B_0(x,y) &= \hat{B}_0 + \tilde{B}_0\hat{b} \\
B_1(x,y) &= \hat{B}_1 + \tilde{B}_1\hat{b} \\
B_2(x,y) &= \hat{B}_2 + \tilde{B}_2\hat{b} \ . \qquad (2.148)
\end{aligned}$$

Therefore equation (2.113) becomes

$$(\hat{B}_2 + \tilde{B}_2\hat{b})\hat{b}^2 + (\hat{B}_1 + \tilde{B}_1\hat{b}) + (\hat{B}_0 + \tilde{B}_0\hat{b}) = 0 \ . \tag{2.149}$$

Organizing the terms as a polynomial in $\hat{b}$ we obtain Theorem 8.

□

2.4 Discussion

In this section, we examined a mechanism proposed in Burroughs et al. (2006), also presented in Burroughs et al. (2008, 2011a,b) and reviewed in Pinto et al. (2010) of Treg control of immune responses through regulation of cytokine dependent T cell proliferation. In particular, we studied here the asymmetry introduced in Burroughs et al. (2011b).

When we analyse the model with asymmetry in the absence of Tregs we already observe an hysteresis, similar to the result presented in Burroughs et al. (2006). This is shown by the approximate formula in Theorem 1 and the exact formula in the Theorem 2.

In Theorems 3 and 4, we determine analytic formulas that describe approximately and exactly, respectively, the fine balance between Regulatory T cells and T cells, in particular at controlled and immune response equilibrium states. We observe that, for the parameter values chosen, the maximum concentration of Tregs is found for concentrations of T cells around $10^4 - 10^5$. At these values, there is enough secretion of IL-2 cytokine by T cells to sustain a larger population of Tregs and the balance between growth and death is favourable to the Tregs. For lower concentrations of T cells, there is not enough cytokine to sustain larger populations of Tregs; for higher concentrations of T cells the growth rate of Tregs is insufficient to overcome the increase in the fas-fasL death rates due to the increase in the population of the T cells.

In Theorems 5 and 6, we determine explicit formulas that relate approximately and exactly, respectively, the antigenic stimulation of T cells, the concentration of T cells and the concentration of Tregs. For our parameter values, we observe that the relation between the antigenic stimulation of T cells and the concentration of T cells is an hysteresis. There is a controlled state for antigenic stimulations b of T cells below b_L, an immune response state for antigenic stimulations b of T cells above b_H and a bistability region for b between b_L and b_H, as found in the symmetric case in Burroughs et al. (2006, 2008). By changing some of the parameters, it is possible to reach a cusp bifurcation point, where a drastic change in the dynamical behavior occurs: the unfold of the hysteresis. The hysteresis is unfolded when the homeostatic concentration of T

cells T_{hom} is high enough to override the control structure constituted by the thresholds b_L and b_H. This happens when T_{hom} rises to values only attained before when the antigenic stimulation of T cells was close to b_L. The unfold of the hysteresis is already present in model with symmetry, see Burroughs et al. (2006, 2008), here we observe that it unfolds for large values of $\frac{d_R}{d_T}$, $\frac{d_{T^*}}{d_T}$ and $\frac{d_{R^*}}{d_R}/\frac{d_{T^*}}{d_T}$. For low values of $\frac{R_{input}}{T_{input}}$ the hysteresis shrinks but does not unfold.

The correlation between the antigenic stimulation b of T cells and the antigenic stimulation a of Tregs was modeled by the linear relation from Burroughs et al. (2011b) to simulate the effect of the antigen presenting cells. In Theorems 7 and 8 we present explicit formulas that relate the approximate and exact relation between the antigenic stimulation of T cells with the concentration of Tregs y and the concentration of T cells x. These formulas are polynomials of third order in b. By contrast, the formulas from Theorems 5 and 6, are linear and quadratic in b, respectively. Therefore, when we consider this tuning it may be possible to find three solutions where only one or two solutions would be found. Therefore, Theorems 7 and 8 are able to explain the appearance of an isola and the transcritical bifurcation that occurs in Burroughs et al. (2011b).

To conclude, in this section we analysed the model considering an asymmetry in the death rates, thus contributing to depthen the understanding of the immune response by T cells. We have obtained approximate formulas for the equilibria (stable or unstable); afterwards, we improved these results to attain exact formulas. These analytic formulas relate the concentration of T cells, the concentration of Tregs and the antigenic stimulation of T cells without and with the presence of a tuning between the antigenic stimuli.

Chapter 3

Optimal investments in Cournot competition

3.1 Introduction

We consider a Cournot competition model Cournot (1897), where two firms invest in R&D projects to reduce their production costs Ferreira et al. (2008); Pinto et al. (2008). This competition is modeled, as usual, by a two stages game see d'Aspremont and Jacquemin (1988). In the first subgame, two firms choose, simultaneously, the R&D investment strategies to reduce their initial production costs and in the second subgame, the two firms are involved in a Cournot competition with production costs equal to the reduced cost obtained in the previous stage. We find the strategic optimal equilibra for the two stages game and study the economical impacts resulting from having distinct equilibria, see Brander and Spencer (1983); Ruff (1997). As it is well known, the second subgame, consisting of a Cournot competition, has a unique Nash equilibrium. For the first subgame, consisting of an R&D investment program there are at most three distinct types of strategic optimal investment equilibria: (i) a Nash equilibrium where both firms invest, see d'Aspremont and Jacquemin (1988); (ii) a Nash equilibrium where firm F_1 invests and firm F_2 does not; (iii) a Nash equilibrium where firm F_2 invests and firm F_1 does not. We consider a competitive investment region C where both firms invest, a single investment region S_1 for firm F_1 where just firm F_1 invests, and a single investment region S_2 for firm F_2 where just firm F_2 invests. We observe that these regions can have non-empty intersections, i.e. the strategic optimal investment equilibrium might not be unique.

As in Ferreira et al. (2009, 2010), we construct a discrete time evolution on the production costs that we call *(myopic optimal) discrete R&D dynamics*, as follows: given

a pair of production costs $(c_1(n), c_2(n))$, at time n, each strategic optimal investment equilibrium $(v_1(n), v_2(n))$ determines a new pair of production costs $(c_1(n+1), c_2(n+1))$, at time $n+1$. The discrete R&D dynamics in the production costs $(c_1(n), c_2(n))$, determines discrete R&D dynamics in the strategic optimal investment equilibrium $(v_1(n), v_2(n))$ and in the profits $(\pi_1(n), \pi_2(n))$ of the firms. We observe that the map from the production costs at time n to the production costs at time $n+1$ might be multi-valued. Furthermore, we construct a *(myopic optimal) continuous R&D dynamics* on the investments $(v_1(t), v_2(t))$ where each firm chooses its marginal rate of investment proportional to the marginal rate of the profit with respect to its investment. The continuous R&D dynamics in the investments $(v_1(t), v_2(t))$ determines continuous R&D dynamics in the production costs $(c_1(t), c_2(t))$ and in the profits $(\pi_1(t), \pi_2(t))$ of the firms. The multi-valued indeterminacy in the discrete R&D dynamics is resolved in the continuous R&D dynamics by knowing the initial investments of both firms. The continuous R&D dynamics show the existence of evolutions in the production costs that are omitted in the discrete R&D dynamics. Furthermore we show for the continuous R&D dynamics, that the economic success or failure of a firm can be very sensitive to the initial R&D investment strategies of that firm.

3.2 R&D investments on costs

The Cournot competition with R&D investment programs consists of two subgames in one period of time, see d'Aspremont and Jacquemin (1988); Ferreira et al. (2009). The first subgame is an R&D investment program, where both firms have initial production costs and choose, simultaneously, their R&D investment strategies to obtain new production costs. The second subgame is a typical Cournot duopoly competition with production costs equal to the reduced cost determined in the previous stage.

3.2.1 The R&D program

We consider an economy with a monopolistic sector with two firms, F_1 and F_2, each one producing a differentiated good. Let q_i be the quantity produced by the firm F_i. In the region of quantity space where prices are positive, we assume that the inverse demands are linear and the price p_i of the good produced by the firm F_i is given by

$$p_i = \alpha_i - \beta_i q_i - \gamma q_j,$$

where $\alpha_i, \beta_i > 0$. Furthermore, we assume that the goods are substitutes, i.e. $\gamma > 0$ (see Singh and Vives (1984)).

The firm F_i invests an amount v_i in an R&D program, studied in d'Aspremont and Jacquemin (1988); Qiu (1997) $a_i : [0, (c_i/\lambda_i - \theta_i v_j)^2] \to [0, c_i]$ that reduces its production cost to a new production cost a_i given by

$$a_i(v_i) = c_i - \lambda_i \sqrt{v_i + \theta_i v_j}. \tag{3.1}$$

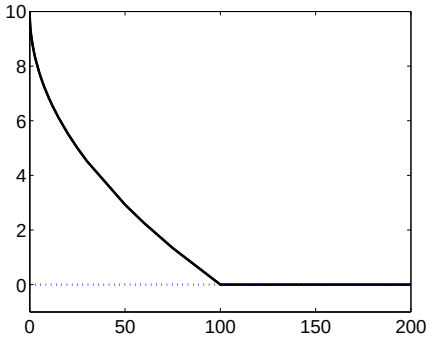

Figure 3.1: R&D investment function, where$\lambda_i > 0$ is a "measure"of the efficiency of the R&D program and $0 < \theta < 1$ is the spillover effect.

All the results presented hold in an open region of parameters $(\lambda_i, \alpha_i, \beta_i, \gamma_i, \theta_i, \theta_j)$ containing the point $(0.2, 10, 0.013, 0.013, 0, 0)$.

3.2.2 Optimal output levels

The profit $\pi_i(q_i, q_j)$ of firm F_i is given by:

$$\pi_i(q_i, q_j) = q_i \left(\alpha_i - \beta_i q_i - \gamma q_j - a_i\right) - v_i, \tag{3.2}$$

for $i, j \in \{1, 2\}$ and $i \neq j$.

The *Nash equilibrium output level* (q_1^*, q_2^*) is given by:

$$q_i^* = \begin{cases} 0, & \text{if } \ R_i \leq 0 \\ R_i, & \text{if } \ 0 < R_i < \frac{\alpha_j - a_j}{\gamma} \\ \frac{\alpha_i - a_i}{2\beta_i}, & \text{if } \ R_i \geq \frac{\alpha_j - a_j}{\gamma} \end{cases}, \tag{3.3}$$

where

$$R_i = \frac{2\beta_j \alpha_i - \gamma \alpha_j - 2\beta_j a_i + \gamma a_j}{4\beta_i \beta_j - \gamma^2},$$

with $i, j \in \{1, 2\}$ and $i \neq j$, see Ferreira et al. (2009, 2010). Hence, (i) if $R_i \leq 0$, the firm F_j is at its monopoly output level; (ii) if $R_i \geq (\alpha_j - a_j)/\gamma$, the firm F_i is at

its monopoly output level; and (iii) if $0 < R_i < (\alpha_j - a_j)/\gamma$, both firms have positive optimal output levels and so firms are facing a duopoly competition. From now on we assume that both firms choose their Nash equilibrium outputs (q_1^*, q_2^*). Thus, firm F_i has profit $\pi_i^*(q_1^*, q_2^*)$ given by:

$$\pi_i^*(q_1^*, q_2^*) = \begin{cases} -v_i, & \text{if } R_i \leq 0 \\ \beta_i R_i^2 - v_i, & \text{if } 0 < R_i < \frac{\alpha_j - a_j}{\gamma} \\ \frac{(\alpha_i - a_i)^2}{4\beta_i} - v_i, & \text{if } R_i \geq \frac{\alpha_j - a_j}{\gamma} \end{cases} . \tag{3.4}$$

3.2.3 New Production costs

Given initial production costs c_1 and c_2, the sets A_i of new production costs for firms F_1 and F_2 are given by:

$$A_i = A_i(c_1, c_2) = [0, c_i],$$

for $i \in \{1, 2\}$. The R&D cost reduction investment programs a_1 and a_2 of the firms determine a bijection between the *investment region* $\mathbb{R}_0^+ \times \mathbb{R}_0^+$ of both firms and the *new production costs region* $A_1 \times A_2$ given by the map

$$\begin{array}{rccc} \mathbf{a} = (a_1, a_2) \ : & \mathbb{R}_0^+ \times \mathbb{R}_0^+ & \longrightarrow & A_1 \times A_2 \\ & (v_1, v_2) & \longmapsto & (a_1(v_1, v_2), a_2(v_1, v_2)), \end{array}$$

where

$$a_i(v_1, v_2) = a_i(v_1, v_2; c_1, c_2) = c_i - \lambda_i \sqrt{v_i + \theta_i v_j}.$$

We denote the inverse map of $\mathbf{a}$ by $\omega = (\omega_1, \omega_2) : \mathbf{a}\left(\mathbb{R}_0^+ \times \mathbb{R}_0^+\right) \to \mathbb{R}_0^+ \times \mathbb{R}_0^+$

$$\omega_i(a_i, a_j) = \left(\left(\frac{(c_i - a_i)}{\lambda_i} \right)^2 - \theta_i \left(\frac{(c_j - a_j)}{\lambda_j} \right)^2 \right) / (1 - \theta_i \theta_j).$$

The new production costs region can be decomposed, at most, in three disconnected economical regions characterized by the optimal output level of the firms:

M_i The *monopoly region* M_i of firm F_i characterized by the optimal output level of firm F_i being the monopoly output and consequently the optimal output level of firm F_j is zero;

D The *duopoly region* D characterized by the optimal output levels of both firms being non-zero and consequently below their monopoly output levels.

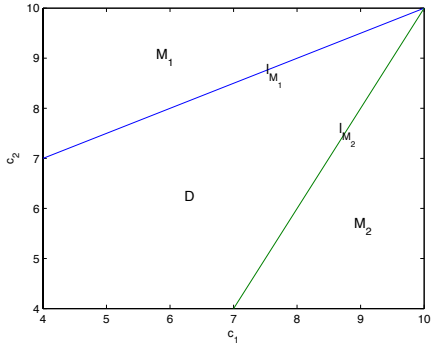

Figure 3.2: New production costs region. Monopoly, M_1, M_2 and duopoly regions, D .

The boundary l_{M_i} between the duopoly region D and the monopoly region M_i is characterized as follows: l_{M_1} is the segment line $a_2 = \gamma(a_1 - \alpha_1)/2\beta_1 + \alpha_2$ and l_{M_2} is the segment line $a_2 = 2\beta_2(a_1 - \alpha_1)/\gamma + \alpha_2$.

Using the Nash output levels for the new production costs (a_1, a_2), the profit function $\pi_i : A_i \times A_j \to \mathbb{R}$ of firm F_i is a piecewise smooth continuous function given by:

$$\pi_i(a_1, a_2) = \begin{cases} \pi_{i,M}, & \text{if } (a_1, a_2) \in M_i \\ \pi_{i,D}, & \text{if } (a_1, a_2) \in D \\ -\omega_i(a_1, a_2), & \text{if } (a_1, a_2) \in M_j \end{cases},$$

where:

$$\pi_{i,M} = \pi_{i,M}(a_1, a_2; c_1, c_2) = \frac{(\alpha - a_i)^2}{4\beta} - \omega_i(a_1, a_2)$$

and

$$\pi_{i,D} = \pi_{i,D}(a_1, a_2; c_1, c_2) = \frac{\beta\left(2\beta(\alpha - a_i) - \gamma(\alpha - a_j)\right)^2}{\left(4\beta^2 - \gamma^2\right)^2} - \omega_i(a_1, a_2).$$

3.2.4 Optimal R&D investment response functions

The *optimal investment response function* $V_1(v_2) = V_1(v_2; c_1, c_2)$ of firm F_1 to a given investment v_2 of firm F_2, is given by:

$$V_1(v_2) = \arg\max_{v_1} \pi_1(a_1(v_1), a_2(v_2)).$$

We will study separately the cases where the new production costs belong to (i) the monopoly region M_1; (ii) the duopoly region D; (iii) the monopoly region M_2.

Let $F_{M_1}(v_2)$ be the set of $v_1 \in \mathbb{R}_0^+$ such that $(a_1(v_1, v_2), a_2(v_1, v_2)) \in l_{M_1}$. Let $Z_{M_1}(v_2)$ be the set of solutions $v_1 \in \mathbb{R}_0^+$ of the following equation

$$\frac{\partial \pi_{1,M_1}}{\partial v_1} = 0$$

satisfying the restriction $(a_1(v_1, v_2), a_2(v_1, v_2)) \in M_1$. We note that $F_{M_1}(v_2)$ and $Z_{M_1}(v_2)$ can be empty. The strategic optimal response $v_1(v_2)$ of firm F_1 in M_1 is given by:

$$v_1(v_2) = \underset{v_1 \in Z_{M_1}(v_2) \cup F_{M_1}(v_2)}{\operatorname{argmax}} \pi_{1,M_1}(a_1(v_1, v_2), a_2(v_1, v_2)).$$

We have the similar definitions for firm F_2.

Lemma 3. *The set $Z_{M_i}(v_j)$ has a unique element*

$$v_i = \min \left\{ \left(\frac{\lambda_i(\alpha_i - c_i)}{4\beta_i - \lambda_i^2} \right)^2, \left(\frac{c_i}{\lambda_i} \right)^2 \right\}$$

if $(a_1(v_1, v_2), a_2(v_1, v_2)) \in M_i$; otherwise, $Z_{M_i}(v_j) = \emptyset$.

Proof: We have

$$\frac{\partial \pi_{i,M}}{\partial a_i} = \frac{(a_i - \alpha_i)}{2\beta_i}, \frac{\partial a_i}{\partial v_i} = -\frac{\lambda_i}{2\sqrt{v_i}}, \frac{\partial \pi_i}{\partial v_i} = -1.$$

Thus,

$$\frac{d\pi_{i,M}}{dv_i} = \frac{(\alpha_i - a_i)}{2\beta_i} \frac{\lambda_i}{2\sqrt{v_i}} - 1 = \frac{\lambda_i(\alpha_i - a_i)}{4\beta_i\sqrt{v_i}} - 1.$$

Hence, $d\pi_{i,M}/dv_i = 0$ iff

$$v_i = \left(\frac{\lambda_i(\alpha_i - c_i)}{4\beta_i - \lambda_i^2} \right)^2.$$

□

Let $Z_{D_1}(v_2)$ be the set of zeros v_1 of the following polynomial

$$\frac{\partial \pi_{1,D}}{\partial v_1} = 0$$

satisfying the restriction $(a_1(v_1, v_2), a_2(v_1, v_2)) \in D$. We note that the set $Z_{D_1}(v_2)$ can be empty. The strategic optimal response $v_1(v_2)$ of firm F_1 in D is given by:

$$v_1(v_2) = \underset{v_1 \in Z_D(v_2) \cup F_{M_1}(v_2)}{\operatorname{argmax}} \pi_{1,D}(a_1(v_1, v_2), a_2(v_1, v_2)).$$

We have the similar definitions for firm F_2.

Let $W_i = \sqrt{v_i + \theta_i v_j}$, $O_i = -4\beta_i\beta_j/(4\beta_i\beta_j - \gamma^2)^2$,

$$\begin{aligned} f_1(W_i, W_j) &= W_j^2 \left(2\beta_j\gamma\lambda_i\lambda_j O_i\right) + W_i W_j \left(-4\beta_j^2\lambda_i^2 O_i - 4\beta_j\right) + \\ &+ W_j \left(2\beta_j\gamma O_i(\alpha_j - c_j) - 4O_i\beta_j^2(\alpha_i - c_i)\right), \end{aligned}$$

and

$$\begin{aligned} f_2(W_i, W_j) &= W_i^2 \left(2O_i\gamma\lambda_i\lambda_j\beta_j\right) + W_i W_j \left(-O_i\gamma^2\lambda_j^2\right) + \\ &+ W_i(2O_i\gamma\beta_j\lambda_j(\alpha_i - c_i) - O_i\gamma^2\lambda_j(\alpha_j - c_j)). \end{aligned}$$

Lemma 4. *$Z_{D_i}(v_j)$ is the set of all zeros $v_i \in [0, (c_i/\lambda_i - \theta_i v_j)^2]$ of the polynomial*

$$f_1(W_i, W_j) + \theta_j f_2(W_i, W_j) = 0 \tag{3.5}$$

with the property that $(a_1(v_1, v_2), a_2(v_1, v_2)) \in D$.

Proof: We have $\partial a_i/\partial v_i = -\lambda_i/(2W_i)$, $\partial a_j/\partial v_i = -(\lambda_j\theta_j)/(2W_j)$, $\partial\pi_{i,D}/\partial v_i = -1$,

$$\begin{aligned} \frac{\partial\pi_{i,D}}{\partial a_i} &= -\frac{4\beta_i\beta_j\left(2\beta_j(\alpha_i - a_i) + \gamma(a_j - \alpha_j)\right)}{\left(4\beta_i\beta_j - \gamma^2\right)^2} \\ &= 2O_i\beta_j(\alpha_i - c_i) + 2\beta_j\lambda_i O_i W_i - \gamma O_i(\alpha_j - c_j) - \gamma\lambda_j O_i W_j \end{aligned}$$

and

$$\begin{aligned} \frac{\partial\pi_{i,D}}{\partial a_j} &= \frac{2\beta_i\gamma\left(2\beta_j(\alpha_i - a_i) + \gamma(a_j - \alpha_j)\right)}{\left(4\beta_i\beta_j - \gamma^2\right)^2} \\ &= -O_i\gamma(\alpha_i - c_i) - O_i\gamma\lambda_i W_i + \frac{O_i\gamma^2}{2\beta_j}(\alpha_j - c_j) + \frac{O_i\gamma^2\lambda_j}{2\beta_j}W_j. \end{aligned}$$

Using the chain rule,

$$\begin{aligned} \frac{d\pi_{i,D}}{dv_i} &= \left(2O_i\beta_j(\alpha_i - c_i) + 2\beta_j\lambda_i O_i W_i - \gamma O_i(\alpha_j - c_j) - \gamma\lambda_j O_i W_j\right)\left(-\frac{\lambda_i}{2W_i}\right) + \\ &+ \left(-O_i\gamma(\alpha_i - c_i) - O_i\gamma\lambda_i W_i + \frac{O_i\gamma^2}{2\beta_j}(\alpha_j - c_j) + \frac{O_i\gamma^2\lambda_j}{2\beta_j}W_j\right)\left(-\frac{\lambda_j\theta_j}{2W_j}\right) - 1. \end{aligned}$$

Hence, $d\pi_{i,D}/dv_i = 0$ iff

$$\begin{aligned} & W_j^2 \left(2\beta_j\gamma\lambda_i\lambda_j O_i\right) + W_i W_j \left(-4\beta_j^2\lambda_i^2 O_i - 4\beta_j\right) + \\ &+ W_j \left(2\beta_j\gamma O_i(\alpha_j - c_j) - 4O_i\beta_j^2(\alpha_i - c_i)\right) + \\ &+ \theta_j(W_i^2 \left(2O_i\gamma\lambda_i\lambda_j\beta_j\right) + W_i W_j \left(-O_i\gamma^2\lambda_j^2\right) + \\ &+ W_i(2O_i\gamma\beta_j\lambda_j(\alpha_i - c_i) - O_i\gamma^2\lambda_j(\alpha_j - c_j)) = 0. \end{aligned}$$

□

The firm F_i uses a patent if $\theta_j = 0$. Let $W_i = \sqrt{v_i}$.

Lemma 5. *Suppose that both firms use patents. $Z_{D_i}(v_j)$ is the set of all zeros $v_i \in [0, (c_i/\lambda_i)^2]$ of the polynomial*

$$\begin{aligned} & W_j^2\left(2\beta_j\gamma\lambda_i\lambda_j O_i\right) + W_i W_j\left(-4\beta_j^2\lambda_i^2 O_i - 4\beta_j\right) + \\ + \;& W_j\left(2\beta_j\gamma O_i(\alpha_j - c_j) - 4O_i\beta_j^2(\alpha_i - c_i)\right) = 0 \end{aligned} \tag{3.6}$$

with the property that $(a_1(v_1, v_2), a_2(v_1, v_2)) \in D$.

Proof: From (3.5), making $\theta_i = \theta_j = 0$ we get (3.6).

□

We note that the strategic optimal response $v_i(v_j)$ of firm F_i with $(a_1(v_1, v_2), a_2(v_1, v_2) \in M_j$ is zero, i.e. not investing.

Theorem 9. *The strategic optimal investment response function $V_i : \mathbb{R}_0^+ \to \mathbb{R}_0^+$ of firm F_i is computed by*

$$V_i(v_j) = \arg \max_{v_i \in R(v_j)} \pi_i(a_1(v_1, v_2), a_2(v_1, v_2)),$$

where $R(v_j) = Z_{M_i}(v_j) \cup F_{M_i}(v_j) \cup Z_{D_i}(v_j) \cup \{0, (c_i/\lambda_i - \theta_i v_j)^2\}$.

Theorem 9 gives an explicit computational algorithm to find the strategic optimal investment response function $V_i : \mathbb{R}_0^+ \to \mathbb{R}_0^+$ that we will use in all the examples discussed in this paper: Using l_{M_1} and l_{M_2}, we know the domains D, M_1 and M_2 and so the set $F_{M_i}(v_j)$. Using Lemma 3, we find $Z_{M_i}(v_j)$. We find the zeros v_i of (3.5), and using l_{M_1} and l_{M_2}, we check if the zeros v_i determine pairs (v_1, v_2) of investments in D. Applying Lemma 4, $Z_{D_i}(v_j)$ is the set of these zeros v_i whose corresponding pairs $(v_1, v_2) \in D$. Finally, comparing the profit values for the investments in $Z_{M_i}(v_j) \cup F_{M_i}(v_j) \cup Z_{D_i}(v_j) \cup \{0\}$, we determine the strategic optimal investment v_i for firm F_i not necessarily unique.

Proof: Theorem 9 follows from lemmas 3 and 4.

□

3.3 Strategic Optimal investment equilibria

Given production costs $(c_1, c_2) \in [0, \alpha_1] \times [0, \alpha_2]$, the *strategic optimal investment equilibria (Nash equilibria)* $(v_1, v_2) \in \mathbb{R}_0^+ \times \mathbb{R}_0^+$ are the solutions of the system:

$$\begin{cases} v_1 = V_1(v_2; c_1, c_2) \\ v_2 = V_2(v_1; c_1, c_2) \end{cases},$$

where V_1 and V_2 are the strategic optimal investment response functions computed in the previous section. Let $N(c_1, c_2)$ be the set of all strategic optimal investment equilibrium for production costs (c_1, c_2).

We find, at most, three distinct types of strategic optimal investment equilibria (v_1, v_2): (i) a *competitive Nash equilibrium* where both firms invest, see d'Aspremont and Jacquemin (1988), i.e. $v_1 > 0$ and $v_2 > 0$; (ii) a *single Nash equilibrium of firm* F_1 where firm F_1 invests and firm F_2 does not, i.e. $v_1 > 0$ and $v_2 = 0$; (iii) a *single Nash equilibrium of firm* F_2 where firm F_2 invests and firm F_1 does not, i.e. $v_2 > 0$ and $v_1 = 0$. We define a *competitive investment region* C consisting of strategic optimal investment equilibria where both firms invest, a *single investment region* S_1 for firm F_1, consisting of strategic optimal investment equilibria where just firm F_1 invests and a *single investment region* S_2 for firm F_2, consisting of strategic optimal investment equilibria where just firm F_2 invests. We say that a firm F_j is out of the market if the output level q_j is zero.

Lemma 6. *Suppose that firm F_i uses a patent. The single Nash equilibrium of firm F_i in the single region S_i drives the other firm F_j out of the market. Furthermore,*

$$v_i = \min\left\{\left(\frac{\lambda_i(\alpha_i - c_i)}{4\beta_i - \lambda_i^2}\right)^2, \left(\frac{c_i}{\lambda_i}\right)^2\right\}$$

is the Nash investment equilibrium of Firm F_i.

Proof: If the Firm F_j is not out of the market then its profit increases if the firm invests because $\partial a_j / \partial v_j(0) = +\infty$. Then by Lemma 3 we obtain that v_i is the Nash investment equilibrium of Firm F_i.

□

In the example discussed in Figure 3.3, we observe that intersection $S_1 \cap S_2$ between the region S_1 and the region S_2 is non-empty, i.e. the strategic optimal investment equilibrium is not unique.

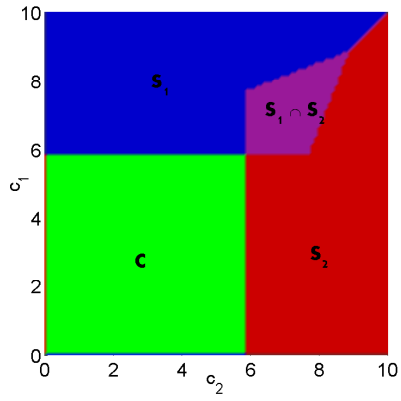

Figure 3.3: Full characterization of the strategic optimal investment regions in terms of the firms' initial production costs (c_1, c_2). The single investment regions S_1 and S_2 are shown in blue and red, respectively. The intersection $S_1 \cap S_2$ between region S_1 and region S_2 is shown in pink. The competitive investment region C is shown in green.

In the example discussed in Figure 3.4, we observe that the firms choose higher values of strategic optimal investments when the production costs take intermediate values. Furthermore, there are a discontinuities in the strategic optimal investments and in the profit function.

3.4 Discrete R&D dynamics

The *(myopic optimal) discrete R&D dynamics*

$$(c_1(n+1), c_2(n+1)) = (g_1(c_1(n), c_2(n)), g_2(c_1(n), c_2(n)))$$

are defined as follows: given a pair of production costs $(c_1(n), c_2(n))$, at time n, each strategic optimal investment equilibrium $(v_1(n), v_2(n)) \in N(c_1(n), c_2(n))$ determines a new pair of production costs

$$(c_1(n+1), c_2(n+1)) = (a_1(v_1(n), v_2(n)), a_2(v_1(n), v_2(n))),$$

at time $n+1$. The discrete R&D dynamics in the production costs $(c_1(n), c_2(n))$, determines discrete R&D dynamics in the strategic optimal investment equilibrium $(v_1(n), v_2(n))$ and in the profits $(\pi_1(n), \pi_2(n))$ of the firms.

We observe that the map from the production costs at time n to the production costs at time $n+1$ is multi-valued when $N(c_1(n), c_2(n))$ is not a singleton. However, we can restrict the analysis separately to (i) the competitive Nash equilibrium in the Duopoly region D; (ii) to the single Nash equilibrium of firm F_1 in the single region S_1; and (iii) to the single Nash equilibrium of firm F_2 in the single region S_2.

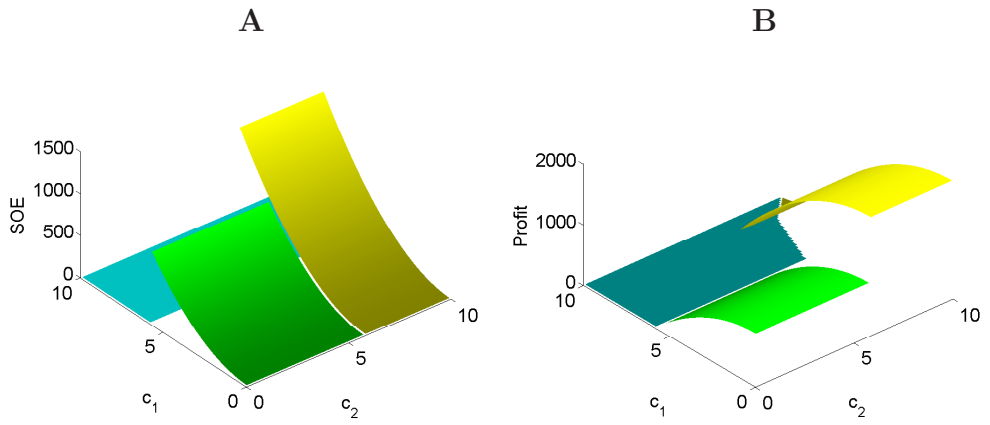

Figure 3.4: 3-D Plots for firm F_1 in terms of the firms' initial production costs (c_1, c_2). Green corresponds to pairs of production costs (c_1, c_2) in the competitive investment region C; Yellow corresponds to pairs of production costs (c_1, c_2) in the single investment region S_1; Light blue corresponds to pairs of production costs (c_1, c_2) in the single investment region S_2. (**A**) Firms' strategic optimal investments; (**B**) Firms' profits.

Lemma 7. *Suppose that firm F_i uses a patent and it has initial production cost $c_i(1)$. In single Nash equilibrium of firm F_i the production cost $c_i(n+1)$ is given by:*

$$c_i(n+1) = \max\left\{0, c_i(n) - \lambda_i \left|\frac{\lambda_i(\alpha_i - c_i)}{4\beta_i - \lambda_i^2}\right|\right\}.$$

Proof: It follows from applying Lemma 6 to the new production cost $a_i(v_i, v_j)$.

□

Hence, by Lemma 7, in the intersection $S_1 \cap S_2$ of the regions S_1 and S_2 depending on which of the two single Nash equilibria is chosen, the firms will achieve two opposite economic outputs: the firm that does not invest gets out of the market and the other firm reduces to zero its production costs in a finite time.

In Figure 3.5, the arrows indicate the evolution under the R&D discrete dynamics for example in the Section above.

3.5 Continuous R&D dynamics

The *(myopic optimal) continuous R&D dynamics* on the investments $(v_1(t), v_2(t))$ consists of each firm choosing its marginal rate of investment proportional to the

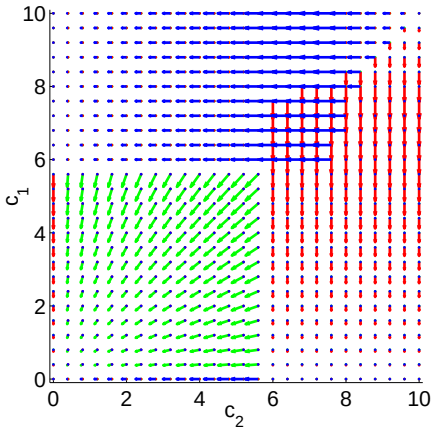

Figure 3.5: Dynamics on the production costs (c_1, c_2): in blue, the dynamics in the single Nash investment region S_1; in red the dynamics in the single Nash investment region S_2; and in green the dynamics in the competitive Nash investment region C.

marginal rate of the profit with respect to its investment

$$\begin{cases} \frac{dv_1}{dt} = \Gamma_1 \frac{\partial \pi_1(c_1,c_2,v_1,v_2)}{\partial v_1} \\ \frac{dv_2}{dt} = \Gamma_2 \frac{\partial \pi_2(c_1,c_2,v_1,v_2)}{\partial v_2} \end{cases} .$$

The continuous R&D dynamics in the investments $(v_1(t), v_2(t))$ determines continuous R&D dynamics in the production costs $(c_1(t), c_2(t))$ and in the profits $(\pi_1(t), \pi_2(t))$ of the firms.

The multi-valued indeterminacy in the discrete R&D dynamics is resolved in the continuous R&D dynamics by knowing the initial investments of both firms.

In the example illustrated in Figures 3.6(**A**) and 3.6(**B**) we observe, for some high initial production costs, that there are close enough initial conditions (v_1, v_2) and (w_1, w_2) whose dynamical evolutions are economically quite distinct: (i) for the initial condition (v_1, v_2) the trajectory of the production costs of both firms F_1 and F_2 go to 0; (ii) for the initial condition (w_1, w_2) the trajectory of the production costs of firm F_1 goes to zero and the firm F_2 goes out of the market. Furthermore, the discrete R&D dynamics can be quite different from the continuous R&D dynamics because for the high production costs considered there is no competitive Nash equilibrium and so case (i) does not occur in the case of discrete R&D dynamics.

3.6 Conclusions

We presented deterministic and stochastic dynamics on the production costs of Cournot competitions, based on perfect Nash equilibria of R&D investment strategies of the

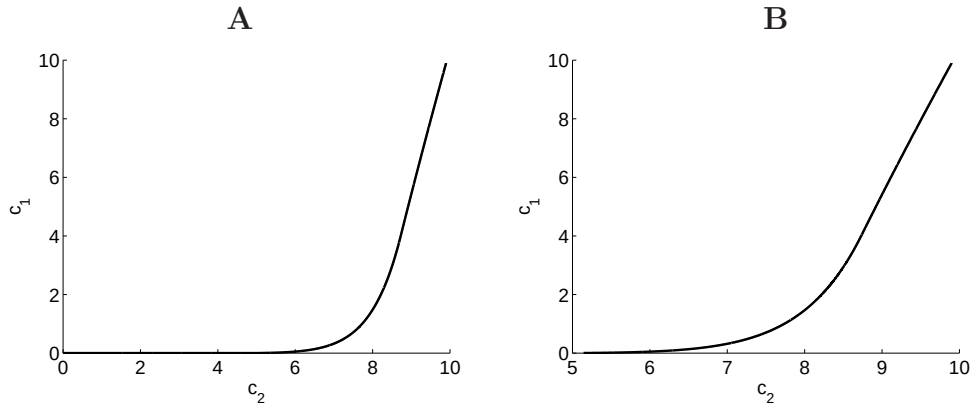

Figure 3.6: Continuous R&D dynamics on the investments. (**A**) Starting at an strategic optimal investment (v_1, v_2); (**B**) Slightly changing the previous strategic optimal investment to (w_1, w_2).

firms at every period of the game. The following conclusions are valid in some parameter regions of our model of Cournot competition for firms with different values of the maximum percentage of reduction of the production costs. The model presented a unique perfect Nash equilibrium, except for initial costs far away from the minimum attainable reduced production costs where the uniqueness of the equilibrium is broken. We characterized the effect of the production costs on the perfect Nash investment equilibria and on the corresponding profits. We described three main economic regions corresponding to drastically distinct, long term, behaviours for the firms along the time: the no survival, weak survival and recovery regions. The boundaries of these regions are described using the stable manifolds of well characterized fixed points showing a nice interplay between dynamical systems, game theory and industrial organization. We illustrated the transients and the asymptotic limits of the deterministic dynamics on the production costs of the duopoly competition. The firm with better R&D program can start with initial higher production costs and recover along the time to be the firm with lower production costs after some periods of time. We have shown drastic long term economic effects resulting from small changes of the maximum percentage of reduction of the production costs of the R&D investment programs, and from small changes of the initial costs of the firms. We observe, for given initial costs for both firms, that the presence of uncertainty in the model allows the firms to have opposite outcomes with positive probability: (i) for some fixed parameter values of the model, with positive probability, the firm F_1 is driven out of the market or, with positive probability, is able to recover; (ii) for some fixed parameter values of the model, with positive probability, the firm F_1 gets out of the market or, with positive probability, firm F_2 is driven out of the market. We observe that the profits of the firms determined by the deterministic dynamics have values significantly lower than the mean values of the profits obtained in the stochastic simulations due to the non-linear effects.

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